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International Application based on the Patent Co-Operation Treaty

| (51) Int.Cl[6] C07C 215/50, 217/70, 217/48 237/30, 229/38, 323/32, 225/16, 219/28, C07D 295/18, 307/88, 215/12, A61K 31/135, 31/34, 31/47 | A1 | (11) Publication Number WO96/22276 |
|---|---|---|
| | | (46) Publication Date 25th July 1996 |

(21) Application Number PCT/JP96/00086
(22) Application Date 19th January 1996

(30) Priority Claim Data
Application No.7/7670 20th January 1995 Japan

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(81) Designated Countries

AU, BR, CA, CN, FI, HU, JP, KR, MX, NO, NZ, RU, UA, US, VN, European Patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), Eurasia Patent (AZ, BY, KG, KZ, RU, TJ, TM)

Appended Document -
International Search Report

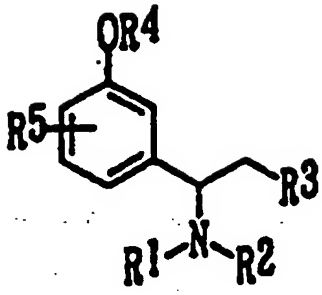
Republished if amendments are received prior to the time limit for amending the Scope of Claims.

(54) **Title of the Invention**

Ethylamine derivatives and drugs

**(57) Abstract**

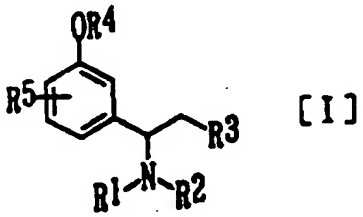
A compound of general formula (I) or a pharmaceutically acceptable salt thereof or its hydrate, wherein $R^1$ and $R^2$ are each independently alkyl or alkenyl; $R^3$ is optionally substituted aryl or an optionally substituted aromatic heterocyclic group having at least one heteroatom selected from the group consisting of nitrogen, oxygen and sulfur in the aromatic heterocycle; $R^4$ is hydrogen, acyl, alkoxycarbonyl or optionally mono- or di-alkyl substituted carbamoyl; and $R^5$ is hydrogen, halogeno or alkyl.




(I)

(57) **Abstract** *{Translated from the Japanese abstract}*

The present invention relates to compounds represented by the following formula [I]




[I]

and their pharmaceutically acceptable salts, or hydrates thereof.

In the formula, $R^1$ and $R^2$ are the same or different and represent alkyl groups or alkenyl groups. $R^3$ represents an optionally-substituted aryl group or an optionally-substituted aromatic heterocyclic group. Said aromatic heterocyclic group contains one or more heteroatoms selected from nitrogen, oxygen and sulphur. $R^4$ represents hydrogen, acyl, alkoxycarbonyl or carbamoyl optionally-substituted with one or two alkyls. $R^5$ represents hydrogen, halogen or alkyl.

Specification

Ethylamine derivatives and drugs

Technical Field

The present invention relates to ethylamine derivatives which have a δ-opioid receptor agonist action and are useful as drugs.

Technical Background

Opioids are described as substances which have morphine-like pharmacological actions and bind to opioid receptors. The opioid receptors are classified into three subtypes (μ, δ and κ) and play a part in inflammation and immunity, blood pressure, and cerebroprotection, etc, through these different receptor subtypes. For example, μ opioid receptor agonists have a strong analgesic action, but dependency occurs. It is also known that μ opioid receptor agonists play a part in the suppression of immunity. κ opioid receptor agonists have an analgesic action but there is little dependency, and they are being developed as analgesics. Moreover, it is known that δ opioid receptor agonists, in addition to having an analgesic action, play a part in the promotion of immunity. Furthermore, it has been reported that μ opioid receptors and δ opioid receptors play a part in the central control of urination.

DPDPE is known as a typical example of a peptide agonist with high selectivity for δ opioid receptors but, because it

is decomposed in the body when intravenously injected or orally administered, it is currently only used as a reagent.

As nonpeptide agonists with high selectivity for δ opioid receptors, there are known only the 4-ring SB 205607, TAN-67, the diphenylmethylpiperazinine *{sic}* derivative BW373-U86 and SNC 80, etc.

On the other hand, as an example of a compound resembling the compounds of the present invention, there is known the muscle pain treatment agent Lefetamine hydrochloride ((-)-N,N-dimethyl-1,2-diphenylethylamine hydrochloride) [see Japanese Patent Publication No. 36-24083]. However, in this compound, the phenyl group which is substituted at the ethylamine 1-position is itself unsubstituted. The pharmacological properties of this drug are mainly a local anaesthetic action and an action on the autonomic nervous system.

Moreover, there are known a large number of ethylamine derivatives where the ethylamine 1-position is substituted with catechol or resorcinol and compounds where the amine portion of the ethylamine is either unsubstituted or only mono-alkyl-substituted (see Chem. Abs. 109: 128510; 104: 148472; 93: 95018; 92: 22365; 91: 20149; 90: 48234; 87: 84784; 85: 56544; 85: 185; 84: 180286; 83: 43011; 82: 92943). For example, ethylamine derivatives formed by substitution with catechol or resorcinol at the ethylamine 1-position are known as intermediates for drug manufacture or as adrenergic drugs, etc. Of these, the 3-[1-

(alkylamino)-2-phenethyl]catechol derivatives (CA 92: 22365; 91: 20149; 85: 56544; 85: 185; 83: 43011, etc) and the 3-[1-(alkylamino)-2-phenethyl]resorcinol derivatives (CA 85: 56544, etc) where the amine portion is just mono-alkyl-substituted, are reported to have an adrenergic action, heart inotropic action and lipidolytic action. On the other hand, 3-(1-amino-2-phenethyl)phenol, where the ethylamine 1-position is substituted with the 3-hydroxyphenyl group and the amine portion unsubstituted, is a known intermediate for the manufacture of drugs with an analgesic action, etc (CA 104: 148472; 93: 95018; 87: 84784; 84: 180286). However, ethylamine derivatives in which the 3-position on the phenyl at the ethylamine 1-position is substituted with a hydroxyl, or with an acyloxy, alkoxycarbonyloxy or carbamoyloxy derived therefrom, and at the same time in which the amine portion is di-substituted with alkyls or alkenyls, are completely unknown.

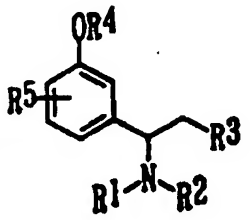
Disclosure of the Invention

An objective of the present invention lay in offering outstanding compounds of novel structure and low toxicity which have an δ-opioid receptor agonist action of high selectivity to δ-opioid receptors.

In order to realise this objective, the present inventors synthesised various compounds of novel structure and, during the course of their investigations, discovered that the compounds represented by the following general formula [I] have an outstanding δ-opioid receptor agonist action and

are of low toxicity. The present invention has been perfected based on this discovery.

Thus, the present invention relates to compounds represented by the following general formula [I]




[I]

and their pharmaceutically acceptable salts, or solvates thereof.

In the formula, $R^1$ and $R^2$ are the same or different, and represent alkyl groups or alkenyl groups. $R^3$ represents an optionally-substituted aryl group or an optionally-substituted aromatic heterocyclic group. Said aromatic heterocyclic group will include at least one heteroatom selected from nitrogen, oxygen and sulphur. $R^4$ represents hydrogen, acyl, alkoxycarbonyl, or optionally mono- or di-alkyl substituted carbamoyl. $R^5$ represents hydrogen, halogen or alkyl.

What characterizes the chemical structure of the compounds of the present invention is that the 3-position on the phenyl at the 1-position on the ethylamine is substituted with hydroxy, or an acyloxy, alkoxycarbonyloxy or carbamoyloxy derived therefrom and, furthermore, at the same time the amine moiety is substituted with identical or different alkyls or alkenyls.

Below, the present invention is explained in detail.

As examples of the alkyls in the present invention, there are those with a straight or branched chain having from 1 to 6 carbons, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, n-hexyl, isohexyl and the like. Of these, those with from 1 to 4 carbons are preferred.

As examples of the alkenyls, there are those with a straight or branched chain having from 2 to 6 carbons, such as vinyl, allyl, isopropenyl, 2-methallyl, 2-butenyl, 3-butenyl and the like. Of these, those with from 2 to 4 carbons are preferred.

As examples of the aryl, there are those with from 6 to 12 carbons, such as phenyl, naphthyl, biphenyl and the like.

As the aromatic heterocyclic group, there can be employed one which is a 5 or 6 membered ring containing at least one heteroatom selected from the nitrogen atom, oxygen atom and sulphur atom, or a condensed such ring, and where linkage is to a carbon atom. As specific examples of the aromatic heterocyclic group, there are 3- or 4-pyridyl, 2-, 3- or 6-benzofuranyl, 2-, 3- or 6- quinolyl, or 5- or 6-benzothienyl, etc.

The aryl or aromatic heterocyclic groups may also have one substituent group or more than one identical or different substituent groups at any positions. As these substituent groups, there are alkyl, aryl, alkoxy, aryloxy, alkylthio, hydroxyalkyl, alkoxyalkyl, trifluoroalkyl, acyl, hydroxy, halogen, cyano, carboxy, optionally halogen-substituted

alkoxycarbonyl, and carbamoyl or sulphamoyl which may be substituted with one substituent or two identical or different substituents selected from the group comprising alkyl, aralkyl and alkoxy. As examples of the alkyl, aryl, alkoxy, aryloxy, alkylthio, hydroxyalkyl, alkoxyalkyl, trifluoroalkyl, acyl, alkoxycarbonyl, aralkyl and halogen which constitute such substituent groups or the groups contained within such substituent groups, there can be cited those described above *{sic}*[i].

As examples of the alkoxy, there are those with a straight or branched chain having from 1 to 4 carbons, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy and the like.

As examples of the aryl of the aryloxy, there can be cited those described above.

Examples of the alkylthio are those with a straight or branched chain having from 1 to 4 carbons, such as methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, sec-butylthio, tert-butylthio and the like.

As examples of the alkyl in the hydroxyalkyl, there can be cited those described above. Specific examples of the hydroxyalkyl are hydroxymethyl, hydroxyethyl, hydroxy-propyl, hydroxybutyl and the like.

As examples of the alkoxyalkyl, there are those with a straight or branched chain having a total of from 2 to 8 carbons, such as methoxymethyl, ethoxymethyl,

methoxypropyl, methoxybutyl, methoxymethyl, methoxybutyl and the like.

As examples of the trifluoroalkyl, there are those with a straight or branched chain having from 1 to 4 carbons such as trifluoromethyl and 2,2,2-trifluoroethyl.

As examples of the acyl, there are formyl, alkanoyl, optionally-substituted aroyl, aralkylcarbonyl and alkenylcarbonyl. As examples of the alkanoyl, there are those with a straight or branched chain having from 1 to 5 carbons, such as acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl and the like. As examples of the aroyl, there are those having from 7 to 11 carbons such as benzoyl and naphthoyl. This aroyl may also be substituted with an amino, alkoxy, halogen or acyloxy. As the aralkyl in the aralkylcarbonyl, there can be cited those described above *{sic}*. As the alkenyl in the alkenylcarbonyl, there can be cited those described above.

As the alkoxy in the alkoxycarbonyl, there can be cited those described above.

As examples of the aralkyl there are those with from 7 to 10 carbons, such as benzyl, phenethyl, phenylpropyl, phenylbutyl and the like.

As examples of the halogen, there are chlorine, fluorine, bromine and iodine.

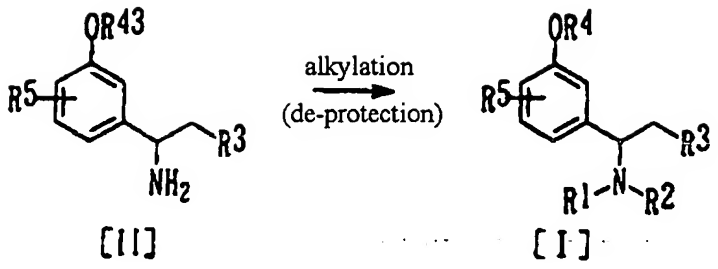
As $R^1$ and $R^2$, $C_{1-4}$ alkyls are preferred, with methyl being particularly preferred. As $R^3$, a substituted aryl is

preferred. Especially preferred is an aryl which has been substituted with an alkoxy, alkoxyalkyl, acyl, alkoxycarbonyl or optionally fluorine-substituted naphthalyl *{sic}*. As $R^5$, hydrogen is preferred. The active form of a compound of the present invention is that where $R^4$ is hydrogen, and so to raise the persistence it is more preferred that this be blocked. In particular, as $R^4$, an acyl, alkoxycarbonyl, or optionally mono- or di-alkyl substituted carbamoyl is preferred.

As examples of the salts of the compounds [I] included in the present invention, there are the salts of inorganic acids such as hydrochloric acid, sulphuric acid, nitric acid, phosphoric acid, hydrofluoric acid or hydrobromic acid, and the salts of organic acids such as acetic acid, tartaric acid, lactic acid, citric acid, fumaric acid, maleic acid, succinic acid, methanesulphonic acid, ethanesulphonic acid, benzenesulphonic acid, toluene-sulphonic acid, naphthalenesulphonic acid, camphor-sulphonic acid and the like. In the case where a carboxy group is present as a substituent, examples of the salts thereof are the salts with metals such as sodium, potassium, calcium or aluminium.

The compounds represented by formula [I] relating to the present invention can be produced, for example, by the following methods.

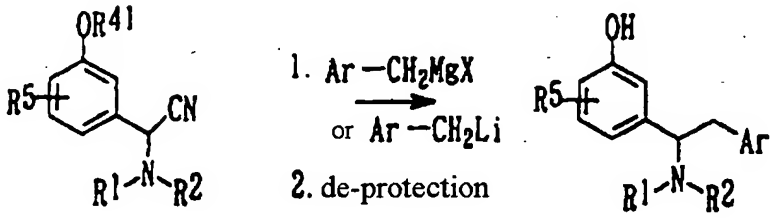
Method A




[II] [I]

(Here, $R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ have the same meanings as above. $R^{43}$ represents $R^4$ or a hydroxyl group protective group.)

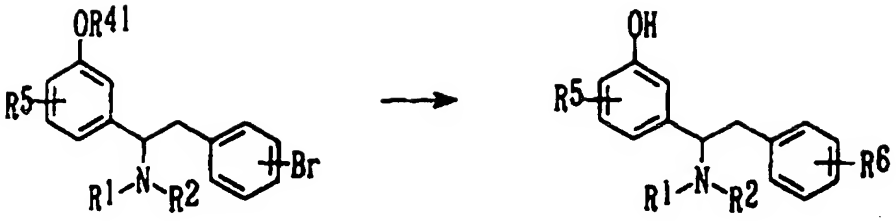
Method B (Case where $R^3$ is an optionally-substituted aryl)




[III] [Ia]

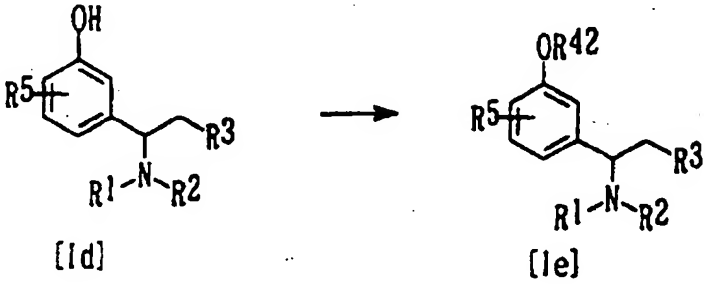
(Here, $R^1$, $R^2$ and $R^5$ have the same meanings as above. $R^{41}$ represents a hydroxyl group protective group, Ar represents an optionally-substituted aryl, and X represents a halogen.)

Method C (Case where $R^3$ is an $R^6$-substituted aryl group)




(Here, $R^1$, $R^2$, $R^5$, $R^{41}$ and X have the same meanings as above. $R^6$ represents alkyl, carboxyl or alkoxycarbonyl.)

Method D (Case where $R^4$ in formula [I] is acyl, alkoxycarbonyl or carbamoyl)




(Here, $R^1$, $R^2$, $R^3$ and $R^5$ have the same meanings as above. $R^{42}$ represents acyl, alkoxycarbonyl or carbamoyl.)

Below, a detailed explanation is given of the methods of production for the case where $R^1$ and $R^2$ are alkyls.

Method A

It is possible to produce compound [I] by subjecting compound [II] to an alkylation reaction and, where necessary, then removing the protective group.

The alkylation reaction of compound [II] can be carried out either by reductively reacting the compound [II] and an aldehyde corresponding to the alkyl represented by $R^1$ or $R^2$ (for example, formaldehyde in the case of methyl, and acetaldehyde in the case of ethyl), or by reaction with an alkylating agent corresponding to the alkyl represented by $R^1$ or $R^2$.

For the reductive alkylation of compound [II] by means of an aldehyde, there is used a method employing a reducing agent or a method based on catalytic reduction, etc.

Alkylation using a reducing agent is normally carried out at -20 to 100°C in a solvent, optionally in the presence of an acid (e.g. an organic acid such as formic acid or acetic acid, or an inorganic acid such as hydrochloric acid or hydrobromic acid). As the reducing agent, there can be used, for example, sodium borohydride, sodium cyanoborohydride, lithium aluminium hydride, lithium borohydride, lithium cyanoborohydride or other such metal hydride compound, or diborane. The solvent will differ according to the reducing agent employed, but there may be used an alcohol such as methanol or ethanol, an ether such as tetrahydrofuran or diethyl ether, or acetonitrile, etc. In regard to the amounts of aldehyde and reducing agent used, normally there will be employed from about 0.5 to about 10 mols per mol of compound [II]. The reaction time will differ according to the starting material, the reducing agent used and the type of solvent, but normally from 0.5 to 24 hours is appropriate.

In the method based on catalytic reduction, normally the reaction is carried out at 0 to 80°C in a solvent, at normal pressure or under applied pressure. As the solvent, there can be used an alcohol such as methanol or ethanol, a carboxylic acid such as acetic acid, an ester such as ethyl acetate, an ether such as dioxane or tetrahydrofuran, or water. Palladium-carbon, Raney nickel or platinum oxide, etc, can be used as the catalyst. From 0.1 to 0.2 mol of catalyst is used per mol of compound [II]. The reaction time will differ depending on the starting material, the catalyst used and the type of solvent, but normally from 0.5 to 48 hours is appropriate.

Further, in the case of a compound where $R^1$ and $R^2$ are both methyl, production can be carried out using from 2 to 5 mols of formaldehyde and formic acid per mol of compound [II], and heating at 50 to 100°C for a period ranging from tens of minutes to several hours.

Alkylation by means of an alkylating agent is normally carried out in a solvent at about 0 to 100°C. As the alkylating agent, there is used an alkyl halide or a dialkyl sulphate corresponding to the aforesaid alkyl group. Examples of the halogen in the alkyl halide are chlorine, bromine and iodine, etc. The amount of alkylating agent used will vary with the particular alkylating agent employed, but it is normally from about 2 to about 2.5 mol per mol of compound [II]. Where required, the reaction can be conducted in the presence of a base to capture the acid produced (examples of which are tertiary amines such as triethylamine, and inorganic bases such as sodium bicarbonate, potassium carbonate and sodium

carbonate, etc). Examples of the reaction solvent are alcohols such as methanol and ethanol, ethers such as tetrahydrofuran, dimethoxyethane, diethyl ether and dioxane, hydrocarbons such as benzene, toluene and xylene, aprotic polar solvents such as N,N-dimethylformamide and dimethylsulphoxide, ketones such as acetone and methyl ethyl ketone, acetonitrile, and solvent mixtures of these. The reaction time will vary according to the starting material, the alkylating agent employed and the type of solvent but, normally, from 30 minutes to 24 hours is suitable.

In the aforesaid alkylation reactions, depending on the type of reducing agent or alkylating agent used, and the reaction conditions, sometimes only one alkyl group is introduced into the amino group of compound [II]. In such circumstances, in order to produce the compound [I] in which two alkyl groups have been introduced, the aforesaid reductive alkylation is again carried out or reaction again carried out with alkylating agent.

It is also possible to employ as the starting material a compound in which the amine moiety is already mono-substituted (in formula [II] either $R^1$ or $R^2$ is an alkyl, while the other is hydrogen).

The hydroxyl group protective group removal reaction can be carried out by a known method.

Method B

[Ia] (the compound where, in formula [I], $R^3$ is an optionally-substituted aryl and $R^4$ is hydrogen) can be produced by reacting a Grignard reagent or a lithium compound with cyano derivative [III], and then eliminating the protective group.

The Grignard reagent or lithium compound can readily be produced by the usual methods. The reaction is carried out at -78°C to 100°C, preferably at -20 to 100°C, in a solvent which is inert to the reaction. As the reaction solvent, anhydrous ether such as tetrahydrofuran, dimethyl ether, diethyl ether, diisopropyl ether, dioxane or dimethoxyethane is most preferred. Otherwise, there can be used a glyme such as ethylene glycol dimethyl ether, or a hydrocarbon such as benzene, toluene, xylene, n-pentane, n-hexane or petroleum ether. These solvents can also be employed as mixtures. The reaction time will vary with the starting material and the type of solvent used but, normally, from 0.5 to 24 hours will be appropriate. There is normally used at least 1 mol and preferably from 1 to 3 mols of the Grignard reagent or lithium compound per mol of the cyano derivative [III].

The hydroxyl group protective group removal reaction can be carried out by a known method.

Method C

It is possible to synthesise compound [Ic] (the compound where, in formula [I], $R^3$ is an alkyl- or aryl-substituted aryl group and $R^4$ is hydrogen) by the reaction of n-butyl lithium with compound [Ib] (the compound where, in formula

[I], $R^3$ is a monobromoaryl group), and reacting an electrophilic reagent with the lithio-derivative produced by halogen-metal exchange, after which the protective group is eliminated. Reaction is carried out at -78°C to 100°C, preferably from -78°C to 25°C, in a solvent which is inert to the reaction. As the reaction solvent, anhydrous ether such as tetrahydrofuran or diethyl ether is preferred. Examples of the electrophilic reagent are ethylene oxide, formaldehyde, alkylaldehyde, dialkyl ketone, N,N-dimethylformamide, acid halide, carbon dioxide, chloroformate ester, nitrate ester, chlorotrialkylsilane, sulphur dioxide, halogen, dialkyl sulphate and the like. The reaction time will vary with the starting material and the type of solvent used, etc, but normally from 0.5 to 24 hours is appropriate. Usually, at least 1 mol and preferably from 1.0 to 1.2 mol of the n-butyl lithium is used per mol of the compound [Ib]. Further, usually at least 1 mol and preferably from 1.0 to 2.0 mols of the electrophilic reagent is used per mol of the compound [Ib].

The hydroxyl group protective group removal reaction can be carried out by a known method.

In aforesaid Methods A to C, the hydroxyl group (where $R^4$ is hydrogen) and the amino group (where $R^1$ and $R^2$ are hydrogen) can, where required, be protected with normally-used protective groups and then, having conducted the aforesaid reactions, the protective groups can be eliminated by a known method. As amino group protective groups, there can be used benzyl, benzyloxycarbonyl or trifluoroacetyl, etc. As hydroxyl group protective groups, there can be used methoxymethyl, 2-methoxyethoxymethyl, methylthiomethyl,

tetrahydropyranyl, t-butyl, benzyl, trimethylsilyl, t-butyldimethylsilyl and the like. In the case where the hydroxyl group is protected with a benzyl group, at the time of catalytic reduction there is simultaneous removal of the benzyl to form a free hydroxyl group.

Method D

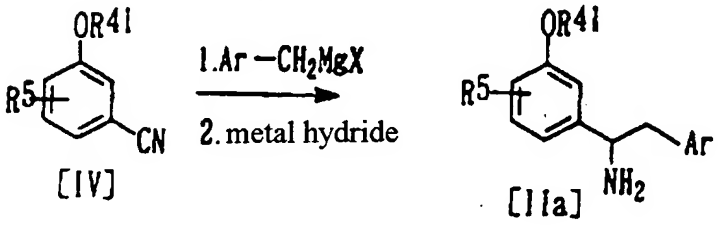
Compound [Ie] can be produced either by the reaction of the phenol derivative [Id] (the compound where, in formula [I], $R^4$ is hydrogen) with an acid halide, acid anhydride or carbamyl halide, etc, in the presence of a base such as sodium hydride, triethylamine or pyridine, etc, or by the reaction with a carboxylic acid or carbamic acid, etc, in the presence of a condensing agent such as DCC (1,3-dicyclohexylcarbodiimide) WSC (water soluble carbodiimide; 1-ethyl-3-(3-dimethylaminopropylcarbodiimde), etc. The reaction is carried out in a solvent such as anhydrous tetrahydrofuran, diethyl ether or other such ether, dichloromethane, chloroform or the like. Reaction is conducted in the range from -40°C to 70°C, and preferably from -20°C to 25°C. The reaction time will vary depending on the starting material and the type of solvent used but, normally, from 0.5 to 24 hours is appropriate. At least 1 mol, and preferably from 1.1 to 1.2 mol, of the base such as sodium hydride, triethylamine, pyridine or the like, or of the condensing agent such as DCC or WSC, is used per mol of the phenol derivative [Id]. At least 1 mol, and preferably from 1 to 2 mols, of the acid halide, acid anhydride, carbamyl chloride, carboxylic acid or carbamic acid is used per mol of the phenolic derivative [Id].

Further, in the case where $R^{42}$ is carbamoyl, [Ie] can also be synthesised by the addition of phenol derivative [Id] to an isocyanate. The reaction is conducted in the absence of solvent or in a solvent such as toluene, benzene, diethyl ether or N,N-dimethylformamide, etc. Reaction is carried out in the range 0°C to 150°C. The reaction time will vary depending on the starting material and the type of solvent used but, normally, from 0.5 to 24 hours is suitable. Acid or base, or cuprous chloride (CuCl), can also be used as a catalyst. At least 1 mol of the isocyanate, and preferably from 1.0 to 1.2 mol, is used per mol of the phenol derivative [Ie] *{sic}*.

In the case where $R^1$ and $R^2$ are alkenyls, it is again possible to produce compound [I] by the same aforesaid alkylation methods. Even where $R^1$ and $R^2$ are different, [I] can be produced by a suitable combination of aforesaid alkylation methods.

Starting materials [II] and [III] are described in reference examples below but can be synthesised as follows.

Production of Starting Material [II]




(Here, $R^5$, $R^{41}$, Ar and X are the same as above.)

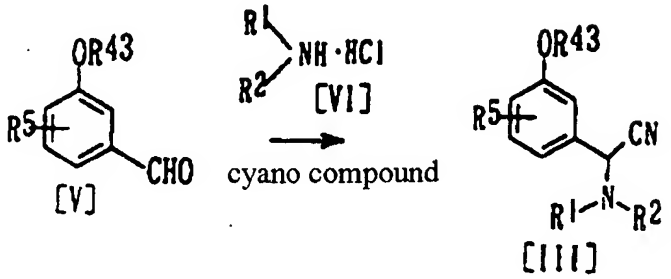
It is possible to produce compound [IIa] (the compound where, in formula [II], $R^3$ is an optionally-substituted aryl and $R^{43}$ is $R^{41}$ (a hydroxyl group protective group)) by the addition of a Grignard reagent or an organolithium reagent to benzonitrile derivative [IV], and then reducing the addition product.

(First stage) The addition reaction of the Grignard reagent or organolithium reagent with the benzonitrile derivative [IV] is carried out in a solvent inert to the reaction, at -78 to 100°C, preferably from -78°C to 50°C. As the reaction solvent, anhydrous tetrahydrofuran, diethyl ether, diisopropyl ether, dioxane, dimethoxyethane or other such ether is most preferred. Otherwise, there can be used a glyme such as ethylene glycol dimethyl ether, or a hydrocarbon such as benzene, toluene, xylene, n-pentane, n-hexane or petroleum ether, etc. These solvents can also be employed as mixtures. The reaction time will vary according to the starting material and the type of solvent employed but, usually, from 0.5 to 10 hours is appropriate. Normally, there is used at least 1 mol, and preferably from 1 to 10 mols, of the Grignard reagent or organolithium reagent per mol of the benzonitrile derivative [IV].

(Second stage) Next, reduction of the addition compound is carried out in the range -78°C to 100°C, in the presence of a reducing agent. As the reducing agent, there can be used a metal hydride compound such as, for example, sodium borohydride, sodium cyanoborohydride, lithium aluminium hydride or lithium borohydride, etc. The amount of reducing agent employed per mol of compound [IV] is normally from 0.5 to 10 mols, and preferably from 1 to 5

mols. The reaction time will vary with the starting material and the type of solvent used but, normally, from 0.5 to 24 hours will be appropriate.

Production of Starting Material [III]

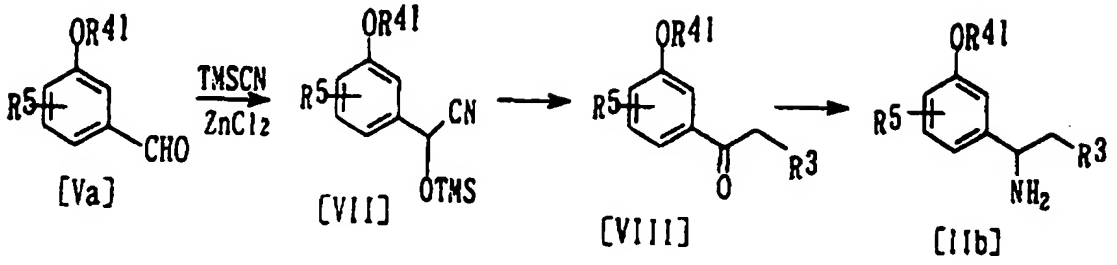



(Here, $R^1$, $R^2$, $R^5$ and $R^{43}$ are the same as above.)

Compound [III] can be produced by the reaction of a cyano compound with benzaldehyde derivative [V] in the presence of amino compound [VI]. The amino compound is employed in the form of the free base or as an acid-added salt, and there is used from 1 to 10 mols per mol of the compound [V]. As the cyano compound, there can be employed, for example, potassium cyanide, sodium cyanide, hydrogen cyanide, copper(I) cyanide or acetone cyanohydrin, etc, and there is used from 1 to 10 mols per mol of compound [V]. As the reaction solvent there can be employed water or an alcohol such as methanol or ethanol, or alternatively a solvent such as dioxane, pyridine, toluene, benzene, ethyl acetate or ether, etc. These solvents can also be used as mixtures. While it will depend on the starting material and the type of solvent used, etc, reaction is conducted within the range 0°C to 100°C, and preferably from 20°C to

80°C, and a reaction time in the range from 1 to 24 hours is appropriate.

Starting material can also be produced by the following method.




(Here, $R^3$, $R^4$, $R^5$ and $R^{41}$ are the same as above. TMS represents trimethylsilyl.)

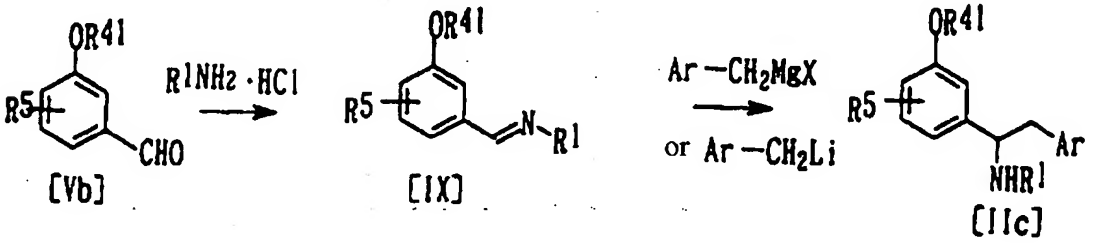
(First stage) Addition product [VII] is obtained when benzaldehyde derivative [Va] is reacted with trimethylsilyl nitrile under a current of argon in the presence of zinc iodide *{sic}*. In regard to this zinc iodide, from 0.01 to 0.1 mol of the catalyst is used per mol of compound [Va]. From 1 to 3 mols of trimethylsilyl nitrile is used per mol of the compound [Va]. As the reaction solvent, there can be employed a solvent such as benzene, toluene or anhydrous tetrahydrofuran, diethyl ether, diisopropyl ether, dioxane, dimethoxyethane or other such ether, etc. These solvents can also be used as mixtures. While it will depend on the starting material and the type of solvent used, etc, reaction is conducted within the range 0°C to 100°C, and preferably from 20°C to 80°C, and a reaction time in the range from 0.5 to 24 hours is appropriate.

(Second stage) Next, the benzyl phenyl ketone derivative [VIII] is obtained by treating the addition product [VII] with a base such as lithium diisopropylamide, etc, and reacting with a benzyl halide derivative, followed by hydrolysis with acid. This reaction is conducted in the range from -78°C to 100°C, and preferably -78°C to 50°C, in a solvent which is inert to the reaction. As the reaction solvent, anhydrous tetrahydrofuran, diethyl ether, diisopropyl ether, dioxane, dimethoxyethane or other such ether is most preferred. These solvents can also be employed as mixtures. The reaction time will vary depending on the starting material and the solvent used but, normally, from 0.5 to 24 hours is appropriate. From 1 to 5 mols, and preferably from 1 to 2 mols, of the base such as lithium diisopropylamide is used per mol of the addition product [VII]. From 1 to 10 mols, and preferably from 1 to 3 mols, of the benzyl halide derivative is used per mol of the addition product [VII]. The hydrolysis by means of the acid is carried out using an excess of 5 to 10% of hydrochloric acid.

(Third stage) It is possible to produce compound [IIb] by the addition of an amine to the benzyl phenyl ketone derivative [VIII] and then performing a reduction reaction. The addition reaction of the amine to the benzyl phenyl ketone derivative [VIII] is carried out in a solvent which is inert to the reaction, at a temperature in the range 0°C to 100°C, preferably from 20°C to 80°C. As the reaction solvent, an alcohol such as methanol, ethanol, propanol, isopropanol or n-butanol is most preferred. These solvents can also be employed as mixtures. There can be used, as the aforesaid amine, ammonium formate, ammonium acetate or

ammonium chloride, etc. The reaction time will vary with the starting material and the type of solvent used but, normally, from 0.5 to 24 hours is appropriate. Usually, at least 1 mol, and preferably from 1 to 10 mols, of the amine will be employed per mol of the benzyl phenyl ketone derivative [VIII]. The addition product reduction reaction is carried out at 20°C to 150°C, in the same kind of solvent as in the aforesaid addition reaction, in the presence of a reducing agent. As the reducing agent, there can be used, for example, a metal hydride such as sodium borohydride, sodium cyanoborohydride, lithium aluminium hydride or lithium borohydride, etc. The amount of reducing agent used per mol of the compound [VIII] will normally be from 0.5 to 10 mols, and preferably from 1 to 5 mols. The reaction time will vary depending on the starting material and the type of solvent used but, normally, from 0.5 to 24 hours will be appropriate.

The starting material in the case where $R^3$ is an aryl can be produced by the following method.



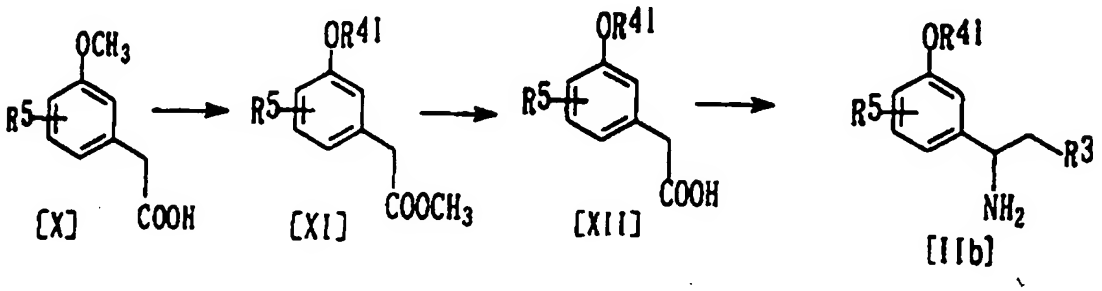

(Here, $R^1$, $R^5$, $R^{41}$ and Ar are the same as above.)

(First stage) It is possible to produce the imine derivative [IX] by the addition of an amine, either in its free base form or in the form of an acid-added salt, to

benzaldehyde derivative [Va] *{sic}*. From 1 to 10 mols of the amine in its free base form or in the form of an acid-added salt will be used per mol of the benzaldehyde derivative [Va]. As the reaction solvent, there can be used water, an alcohol such as methanol or ethanol, or acetonitrile or tetrahydrofuran, etc. These solvents can also be employed as mixtures. While it will differ according to the starting material and the type of solvent used, reaction is carried out in the range from 0°C to 100°C, preferably from 20°C to 80°C, and a reaction time in the range 0.5 to 24 hours is appropriate.

(Second stage) Compound [IIc] can be produced by the addition of a Grignard reagent or an organolithium reagent to the imine derivative [IX]. The addition reaction of the Grignard reagent or organolithium reagent with the imine derivative [IX] is conducted in the range -78°C to 100°C, and preferably -78°C to 50°C, in a solvent which is inert to the reaction. As the reaction solvent, anhydrous tetrahydrofuran, diethyl ether, diisopropyl ether, dioxane, dimethoxyethane or other such ether is most preferred. In addition, there can be used a glyme such as ethylene glycol dimethyl ether, or a hydrocarbon such as benzene, toluene, xylene, n-pentane, n-hexane, petroleum ether or the like. These solvents can also be used as mixtures. The reaction time varies with the starting materials and the type of solvent used but, normally, from 0.5 to 10 hours is appropriate. At least 1 mol, and preferably from 1 to 10 mols, of the Grignard reagent or organolithium reagent is used per mol of the benzaldehyde derivative [Vb].

The starting material, compound [IIb] (the compound where, in formula [II], $R^{43}$ is $R^{41}$ (a hydroxyl group protective group)) can be produced by the following method.




(Here, $R^3$, $R^5$ and $R^{41}$ are the same as above.)

(First stage) Compound [XI] can be derived from the phenylacetic acid derivative [X] by esterification with an alcohol by elimination of water, and then protecting the phenolic hydroxyl group. The use of benzyl, methoxymethyl, methoxyethoxymethyl, or the like, as the protective group is appropriate.

(Second stage) The carboxylic acid derivative [XII] can be obtained from compound [XI] in accordance with the method of Petraganani *et al* [Synthesis, 521 (1982)], by ordinary alkali hydrolysis following the introduction of a substituent at the ester α-position.

(Third stage) The carboxylic acid derivative [XII] is converted to the isocyanate derivative by reaction with diphenyl phosphoryl azide in the presence of a base such as triethylamine. The reaction is preferably carried out in a solvent such as tetrahydrofuran, benzene or toluene, under reflux, for from 1 to 24 hours. The amount of the base and

diphenyl phosphoryl azide used will vary with the starting material, but from 1 to 1.5 mol per mol of compound [XII] is appropriate. Next, benzyl alcohol is added by the method of M.E. Duggan *et al* [Synthesis, 131 (1989)]. By ordinary catalytic reduction of this benzyloxycarbonyl group, there is derived [IIc].

The compounds [I] have an asymmetric carbon, and optical isomers exist. The present invention will encompass all such isomers and their mixtures. Normally a racemic mixture is obtained. Such racemic mixtures will themselves have pharmacological activity but, where desired, they can be separated into the respective isomers. For example, the separation of the isomer mixture can be carried out by known optical resolution methods, such as the method of forming a salt with an optically active carboxylic acid (e.g. (+)- or (-)-tartaric acid, (+)- or (-)-malic acid, or the like) or with an optically active sulphonic acid (e.g. (+)-camphorsulphonic acid, etc) and then performing fractional crystallization, or by a physical separation method using an optically active column. Furthermore, the corresponding isomer [I] can be obtained by employing optically active starting material compounds [II], [III], [Ib] or [Id] (S configuration or R configuration).

The compounds [I] of the present invention can form the aforementioned salts by known methods. For example, the hydrochlorides of the compounds [I] of the present invention can be obtained by dissolving said compounds [I] of the present invention in an alcohol or ethyl acetate solution of hydrogen chloride.

Amongst the compounds [I] of the present invention, those compounds which contain carboxy can form salts by known methods. As examples of the salts, there are the alkali metal salts such as those of sodium or potassium, and the alkaline earth metal salts such as those of calcium, etc. The alkali metal salts of compounds [I] of the present invention, for example, can be obtained by adding an equivalent quantity of sodium hydroxide or potassium hydroxide, etc, to a compound [I] of the present invention which contains a carboxy, preferably in alcohol solution. The alkaline earth metal salts of compounds [I] of the present invention can be obtained by dissolving an alkali metal salt, produced as described above, in water, methanol, ethanol or solvent mixture thereof, and then adding an equivalent amount of calcium chloride, or the like.

Solvates (including the hydrates) of the compounds [I] of the present invention, or of the salts thereof, are also included in the present invention. The solvates can usually be obtained by the recrystallization of the material to be solvated from the corresponding solvent or from a suitable mixed solvent containing the corresponding solvent. For example, the hydrate of a compound [I] of the present invention can be obtained by recrystallization of inventive compound [I] from alcohol containing water.

The compounds [I] of the present invention may exhibit crystal polymorphism. Such crystal polymorphism is also encompassed by the present invention.

A target compound [I] produced in this way can be isolated and purified in the free base form, or in the acid-added salt form or metal salt form, by means which are themselves known, such as concentration, change of pH, solvent exchange, solvent extraction, crystallization, distillation or chromatography, etc.

The compounds of the present invention have a δ-opioid receptor agonist action as described below, so they can be employed as drugs such as analgesics, immunoactivators, anti-aids drugs, urinary frequency/urinary incontinence treatment agents, and the like, with little side effects such as dependency, respiratory depression or constipation, etc.

In cases where a compound of the present invention is to be administered as a drug, said compound of the present invention may be administered to mammals including man as it is, or in a medically approved non-toxic and inactive carrier, for example in a drug composition in which it comprises 0.1% to 99.5%, and preferably from 0.5% to 90%.

There can be used, as the carrier, one or more types of solid, semisolid or liquid diluent, filler or other prescription-use auxiliary. The drug compositions are preferably administered in a unit dose form. The inventive drug compositions can be orally administered, administered into tissue, topically administered (percutaneously administered, etc) or per-rectally administered. Of course administration will be by a dosage form appropriate to the

method of administration. Oral administration, for example, is especially preferred.

It is desirable that the dose as a drug be adjusted taking into consideration the condition of the patient, such as age and bodyweight, etc, the administration route, and the nature and severity of the illness, etc, but normally, for an adult, the daily dose of the effective component of the present invention lies in the range 0.1 μg to 100 mg/person, and preferably from 500 μg to 30 mg/person, when administered orally. Depending on the circumstances, less than this may suffice or, alternatively, a dose greater than this may be necessary. Further, the daily administration can be conducted by sub-division, into two or three administrations per day.

Oral administration can be carried out by means of solid or liquid dosage units, such as powders, dispersed powders, tablets, sugar-coated preparations, capsules, granules, suspensions, solutions, syrups, drops, sublingual tablets and other dosage forms.

Powders are produced by reducing the active material to a suitable fineness. Dispersed powders are produced by reducing the active material to a suitable fineness and then mixing with a medicinal support of similar fineness such as an edible carbohydrate like starch or mannitol, or the like. Where required, there may be included flavourings, preservatives, dispersants, colorants, perfumes and other such materials.

Capsules are produced by introducing powder or dispersed powder firstly produced as described above, or a granular material of the kind discussed in the paragraph on tablets below, into for example a capsule case such as a gelatine capsule. The filling process can also be carried out after mixing the powder/granules with materials such as lubricants and fluidizing agents like, for example, colloidal silica, talc, magnesium stearate, calcium stearate and solid polyethylene glycol. The effectiveness of the drug can be improved at the time of the ingestion of the capsule by the addition of disintegrating agents and solubilizers such as, for example, carboxymethyl cellulose, calcium carboxymethyl cellulose, hydroxypropyl cellulose of low degree of substitution, sodium croscarmellose, sodium carboxymethyl starch, calcium carbonate and sodium carbonate.

Furthermore, soft capsules can be prepared by suspending/dispersing fine powder of the compound [I] in vegetable oil, polyethylene glycol, glycerine or surfactant, and enveloping this with gelatine sheet. Tablets are produced by adding excipient to prepare a powder mixture, after which granulation or slugging is conducted, then a disintegrating agent or lubricant added and tableting carried out. Regarding the powder mixture, suitably powdered material is mixed with an aforesaid diluent or base and, optionally, there may also be jointly employed binders (e.g. sodium carboxymethyl cellulose, methyl cellulose, hydroxypropyl methyl cellulose, gelatine, polyvinyl pyrrolidone, polyvinyl alcohol, etc), dissolution retarders (e.g. paraffin, etc), re-absorption agents (e.g. quaternary salts) and adsorbents (e.g. bentonite, kaolin,

dicalcium phosphate, etc). Powder mixtures can be produced as granules by firstly wetting with a binder, e.g. a syrup, starch paste, gum arabic, cellulose solution or polymer solution, and then stirring/mixing, after which drying and grinding are carried out. Instead of granulating the powder in this way, granules can be produced by first supplying to a tableting machine, and then grinding the imperfectly-formed slugs obtained. The granules thus produced can be prevented from sticking together by adding, as a lubricant, stearic acid, stearate salts, talc, mineral oil or the like. Mixtures which have been lubricated in this way are then tableted. The uncoated tablets thus obtained can be subjected to film coating or sugar coating.

Again, the drug may also be directly tableted after mixing with an inactive fluid carrier, without passing through the aforesaid kinds of granulation or slugging processes. There can also be used transparent or translucent protective coatings consisting of closed coats of shellac, or coatings of sugar or polymer material, and also polished coatings comprising wax. Other oral administration forms such as solutions, syrups, elixirs, and the like, can be produced in the form of dosage units so that a fixed quantity thereof contains a fixed quantity of the drug. Syrups can be produced by dissolving the compound in suitably flavoured aqueous solutions and elixirs can be produced by using non-toxic alcoholic carriers. Suspensions can be formulated by dispersing the compound in non-toxic carriers. Solubilizing agents and emulsifying agents (e.g. ethoxylated isostearyl alcohols and polyoxyethylene sorbitol esters), preservatives, flavour

conferring agents (e.g. peppermint oil and saccharin), and the like, can be added where required.

Optionally, unit dosage formulations for oral administration may also be micro-encapsulated. Again, by coating, or by enveloping in a polymer or wax, the formulation can provide a prolongation of the time of action or continuous release.

In-tissue administration can be carried out by using liquid unit dose forms, like solutions or suspensions, prepared for subcutaneous, intramuscular or intravenous injection. These can be produced by suspending or dissolving a fixed quantity of the compound in a non-toxic liquid carrier suitable for the purposes of injection, e.g. an aqueous or oily solvent, and then sterilizing the suspension or solution. Non-toxic salt or salt solutions may be added for isotonizing the injection fluids. Moreover, there can also be jointly used stabilizers, preservatives and emulsifying agents.

Rectal administration can be conducted using suppositories, or the like, produced by dissolving or suspending the compound in a low-melting water-soluble or water-insoluble solid such as polyethylene glycol, cacao butter, semi-synthetic fats and oils (e.g. Witepsol®), higher esters (e.g. myristyl palmitate), and mixtures thereof.

Optimum Form for Practising the Invention

Next, the present invention is explained in still further detail by providing reference examples and practical

examples relating to the production of the compounds of the present invention, together with experimental examples using typical compounds. Now, the specific rotation was measured at 20°C.

Reference Example 1

(±)-1-[3-(methoxymethoxy)phenyl]-2-(4-methoxyphenyl)-ethylamine

(1) 3-(methoxymethoxy)benzonitrile

5.0 g of 3-cyanophenol and 14.6 ml of N,N-diisopropylethylamine were dissolved in 50 ml of dichloromethane and then, while ice cooling, there was added dropwise a solution of 4.8 ml of chloromethyl methyl ether in 10 ml of dichloromethane, and stirring carried out for 1 hour at room temperature. The reaction liquid was extracted with dichloromethane, washed with 10% aqueous sodium hydroxide solution and with saturated salt solution, and then dried using anhydrous magnesium sulphate, after which the solvent was distilled off. The residue was distilled under reduced pressure, and 6.38 g (93%) of the target compound obtained as a colourless oily material. bp 110-113°C/5 mmHg

(2) (±)-1-[3-(methoxymethoxy)phenyl]-2-(4-methoxyphenyl)-ethylamine

A Grignard reagent prepared from 18.8 g of 4-methoxybenzyl chloride, 2.92 g of magnesium and 100 ml of dry tetrahydrofuran was stirred at room temperature under a current of argon gas, and a solution of 16.3 g of 3-

(methoxymethoxy)benzonitrile in 70 ml of dry tetrahydrofuran added dropwise, after which the mixture was heated to 50°C and stirred for 1 hour. After cooling to room temperature, 4.55 g of lithium aluminium hydride was added divided into five portions, and the stirring continued overnight. Next, ice water was added to the reaction liquid, and ether extraction performed, followed by washing with water and saturated salt solution, and drying with anhydrous magnesium sulphate, after which the solvent was distilled off. The residue was purified by silica gel column chromatography, and 13.9 g of the target compound obtained as a pale yellow oily material.

Reference Example 2

(±)-2-dimethylamino-2-[3-(methoxymethoxy)phenyl]acetonitrile

A mixture of 5.0 g of 3-(methoxymethoxy)benzaldehyde, 2.57 g of dimethylamine hydrochloride and 10 ml of water was stirred at room temperature, and 16 ml of an aqueous solution of 2.15 g of potassium cyanide added dropwise, after which the temperature was raised to 80°C and stirring continued for 2 hours. After cooling, extraction was carried out with ethyl acetate, then washing performed with water and saturated salt solution, followed by drying with anhydrous magnesium sulphate, after which the solvent was distilled off and 5.56 g (84%) of the target compound obtained as an orange oily material.

Reference Example 3

1-[3-(methoxymethoxy)phenyl]-2-(2-naphthyl)ethylamine

(1) 3-(methoxymethoxy)phenyl 2-naphthylmethyl ketone

0.8 g of zinc iodide was added to 160 ml of a dry benzene solution of 26.6 g of 3-(methoxymethoxy)benzaldehyde under a current of argon, and stirring carried out for 15 minutes. Then, 18.4 g of 95% trimethylsilylnitrile was added all in one go, and stirring performed for 1.5 hours. After diluting the reaction liquid by the addition of 50 ml of ether, it was poured into 100 ml of water and the ether layer separated off. The ether layer was washed with water (75 ml × 2), dried with anhydrous magnesium sulphate and the solvent distilled off under reduced pressure. 80 ml of a dry tetrahydrofuran (THF) solution of the pale yellow oily material obtained was added dropwise over 30 minutes, while stirring, to a mixture of 80 ml of dry THF and 88 ml of a 2.0M THF solution of lithium diisopropylamide, which had previously been cooled to -78°C in a dry ice/acetone bath, and then stirring carried out for 1 hour. 80 ml of a dry THF solution of 31.1 g of 2-chloromethylnaphthalene was slowly added dropwise such that the temperature of the reaction liquid did not exceed -55°C and, after stirring for 1 hour, the dry ice/acetone bath was removed and stirring conducted for 2 hours. Next, the reaction liquid was cooled to 0°C, and after slowly adding 240 ml of 10% aqueous hydrochloric acid, the ice bath was removed and stirring carried out overnight. Following the completion of the reaction, the organic layer was removed and the aqueous layer extracted with ether (60 ml × 3). The combined organic layers were washed with 150 ml of water and 150 ml of saturated aqueous $NaHCO_3$ solution, and dried with anhydrous magnesium sulphate, after which the solvent

was distilled off under reduced pressure. The residue obtained (yellow oily material) was purified by silica gel column chromatography (n-hexane : AcOEt = 7 : 1), and 45.4 g of the target material obtained as a yellow oily material (yield 93%).

(2) 1-[3-(methoxymethoxy)phenyl]-2-(2-naphthyl)ethylamine

41 g of ammonium formate was added to 195 ml of a methanol solution of 3-(methoxymethoxy)phenyl 2-naphthylmethyl ketone, and then 8.6 g of 95% sodium cyanoborohydride added while stirring at room temperature. Next, 6.5 ml of formic acid was added dropwise, and the mixture heated and stirred overnight at 60°C. Following the completion of the reaction, the reaction liquid was concentrated to less than half under reduced pressure, then 100 ml of saturated aqueous $NaHCO_3$ solution added, to give a pH of 8, and extraction performed with ethyl acetate (50 ml × 3). After drying with anhydrous magnesium sulphate, the solvent was eliminated under reduced pressure. The yellow oily material obtained was purified by silica gel column chromatography ($CHCl_3$ : MeOH = 50 : 1), and 7.4 g of the target compound obtained as a yellow oily material (yield 37%).

The following compounds were obtained in the same way.

1. (±)-2-(4-biphenyl)-1-(3-methoxymethoxyphenyl)ethylamine

2. (±)-1-(3-methoxymethoxyphenyl)-2-(1-naphthyl)ethylamine

3. (±)-1-(3-methoxymethoxyphenyl)-2-(4-isopropoxyphenyl)-ethylamine

4. (±)-1-(3-methoxymethoxyphenyl)-2-(4-trifluoromethyl-phenyl)ethylamine

5. (±)-2-(4-N,N-diethylcarbamoylphenyl)-1-(3-methoxy-methoxyphenyl)ethylamine

6. (±)-2-(4-carbamoylphenyl)-1-(3-methoxymethoxyphenyl)-ethylamine

7. (±)-2-(4-N,N-dimethylcarbamoylphenyl)-1-(3-methoxy-methoxyphenyl)ethylamine

8. (±)-2-(4-N-ethylcarbamoylphenyl)-1-(3-methoxy-methoxyphenyl)ethylamine

9. (±)-2-(4-N-benzylcarbamoylphenyl)-1-(3-methoxy-methoxyphenyl)ethylamine

10. (±)-1-(3-methoxymethoxyphenyl)-2-(4-phenethyl-carbamoylphenyl)ethylamine

11. (±)-1-(3-methoxymethoxyphenyl)-2-(4-pyrrolidino-carbonylphenyl)ethylamine

12. (±)-2-(4-ethoxycarbonylphenyl)-1-(3-methoxymethoxy-phenyl)ethylamine

13. (±)-2-(4-methoxycarbonylphenyl)-1-(3-methoxymethoxyphenyl)ethylamine

14. (±)-2-(4-isopropoxycarbonylphenyl)-1-(3-methoxymethoxyphenyl)ethylamine

15. (±)-2-[4-(2-fluoroethoxycarbonyl)phenyl]-1-(3-methoxymethoxyphenyl)ethylamine

16. (±)-1-(3-methoxymethoxyphenyl)-2-[4-(2,2,2-trifluoroethoxycarbonyl)phenyl]ethylamine

17. (±)-1-(3-methoxymethoxyphenyl)-2-(phthalid-5-yl)ethylamine

18. (±)-2-(3-ethoxycarbonylphenyl)-1-(3-methoxymethoxyphenyl)ethylamine

19. (±)-2-(4-ethoxycarbonylmethylphenyl)-1-(3-methoxymethoxyphenyl)ethylamine

20. (±)-2-(4-cyanophenyl)-1-(3-methoxymethoxyphenyl)-ethylamine

21. (±)-1-(3-methoxymethoxyphenyl)-2-(4-methylthiophenyl)ethylamine

22. (±)-2-(benzofuran-2-yl)-1-(3-methoxymethoxyphenyl)-ethylamine

23. (±)-1-(3-methoxymethoxyphenyl)-2-(6-methoxy-2-naphthyl)ethylamine

24. (±)-1-(3-methoxymethoxyphenyl)-2-(2-methylbenzofuran-5-yl)ethylamine

25. (±)-1-(3-methoxymethoxyphenyl)-2-(5-methoxybenzofuran-2-yl)ethylamine

26. (±)-1-(3-methoxymethoxyphenyl)-2-(3-trifluoromethyl-phenyl)ethylamine

27. (±)-2-(1-fluoro-2-naphthyl)-1-(3-methoxymethoxy-phenyl)ethylamine

28. (±)-1-(3-methoxymethoxyphenyl)-2-(3-quinolyl)ethylamine

29. (±)-2-(benzofuran-6-yl)-1-(3-methoxymethoxyphenyl)-ethylamine

30. (±)-2-(8-fluoro-2-naphthyl)-1-(3-methoxymethoxyphenyl)-ethylamine

The 2-chloromethyl-8-fluoronaphthalene used as a starting material was obtained as follows.

The Schiemann reaction was carried out on 8-amino-2-naphthol and 8-fluoro-2-naphthol obtained. Next, reaction was performed with anhydrous trifluoromethanesulphonic acid in pyridine solvent and the triflate obtained.

Furthermore, in a mixed methanol, DMSO and 1,2-dichloroethane solution, reaction was conducted with carbon monoxide in the presence of palladium diacetate, DPPP [1,3-bis(diphenylphosphino)propane] and triethylamine, and the methyl 8-fluoro-2-naphthoate ester obtained. This was reduced with diisobutylaluminium hydride and chlorinated with thionyl chloride, to produce the 2-chloromethyl-8-fluoronaphthalene.

31. (±)-2-(4-ethoxymethylphenyl)-1-(3-methoxymethoxy-phenyl)ethylamine

The 4-ethoxymethylbenzyl chloride used as a starting material was synthesised by the reaction between commercial α,α'-dichloro-p-xylene and sodium ethoxide in ethanol solvent.

32. (±)-1-(3-methoxymethoxyphenyl)-2-(4-methoxymethyl-phenyl)ethylamine

33. (±)-2-[4-(2-fluoroethoxymethyl)phenyl]-1-(3-methoxymethoxyphenyl)ethylamine

34. (±)-2-(2,4-dichlorophenyl)-1-(3-methoxymethoxyphenyl)-ethylamine

35. (±)-2-(3,4-dichlorophenyl)-1-(3-methoxymethoxyphenyl)-ethylamine

36. (±)-2-(benzofuran-5-yl)-1-(3-methoxymethoxyphenyl)-ethylamine

37. (±)-2-(4-N,N-dimethylsulphonylphenyl)-1-(3-methoxy-methoxyphenyl)ethylamine *{sic}*

Reference Example 4

N-[3-(methoxymethoxy)benzylidene]methylamine

8.31 g of 3-(methoxymethoxy)benzaldehyde was slowly added to 6.5 ml of 40% aqueous methylamine solution, after which stirring was conducted overnight. The reaction liquid was extracted with ether, washed with saturated salt solution and dried with anhydrous magnesium sulphate, after which the solvent was distilled off. The residue obtained was distilled under reduced pressure, and 7.49 g (84%) of the target compound obtained as a colourless oily material.

Reference Example 5

Optical isomer of 1-[3-(methoxymethoxy)phenyl]-2-(4-methoxyphenyl)ethylamine

(1) Production of (E)-(S)-N-[3-(methoxymethoxy)-benzylidene]valinol

A mixture of 1.66 g of 3-(methoxymethoxy)benzaldehyde, 1.03 g of S-(+)-valinol and 20 ml of benzene was heated under reflux for 8 hours, with a Dean-Stark trap fitted. After cooling, the reaction liquid was distilled under reduced pressure and 2.40 g of the target compound obtained as a yellow oily material (yield 96%).

(2) Production of (1'S)-N-(2'-hydroxy-1'-isopropylethyl)-1-[3-(methoxymethoxy)phenyl]-2-(4-methoxyphenyl)ethylamine

15 ml of a dry tetrahydrofuran solution of 1.25 g of (E)-(S)-N-[3-(methoxymethoxy)benzylidene]valinol was stirred at room temperature under a current of argon, and to this was slowly added a Grignard reagent prepared from 3.92 g of 4-methoxybenzyl chloride, 0.61 g of magnesium and 25 ml of dry tetrahydrofuran, after which heating and stirring were conducted for 15 hours at 60°C. After cooling, an aqueous solution of ammonium chloride was added to the reaction liquid and then extraction performed with ether. After washing with water and saturated salt solution, and then drying with anhydrous magnesium sulphate, the solvent was distilled off. The residue obtained was purified by means of silica gel column chromatography, and 1.47 g of the target compound obtained as a yellow oily material (yield 79%).

(3) Production of optical isomer of 1-[3-(methoxymethoxy)phenyl]-2-(4-methoxyphenyl)ethylamine

28 ml of a 40% aqueous methylamine solution, and then 28 ml of an aqueous solution of 2.19 g of periodic acid dihydrate were slowly added to 28 ml of a methanol solution of 1.40 g of (1'S)-N-(2'-hydroxy-1'-isopropylethyl)-1-[3-(methoxymethoxy)phenyl]-2-(4-methoxyphenyl)ethylamine, and stirring carried out for 30 minutes at room temperature. The reaction liquid was extracted with ether, then washing with water and saturated salt solution conducted, followed by drying with anhydrous magnesium sulphate, after which the solvent was distilled off. The residue obtained was

purified by silica gel column chromatography, and 0.58 g of the target compound obtained as a pale yellow oily material (yield 54%).

Reference Example 6

Optical isomer of 1-[3-(methoxymethoxy)phenyl]-2-(2-naphthyl)ethylamine

(1) Production of 3-(methoxymethoxy)phenyl 2-naphthylmethyl ketone-oxime O-methyl ether

20 ml of an ethanol solution of 18.38 g of 3-(methoxymethoxy)phenyl 2-naphthylmethyl ketone obtained in Reference Example 3(1) was added to 60 ml of an aqueous solution of 5.51 g of O-methylhydroxylamine hydrochloride and 8.98 g of sodium acetate, and then ethanol added to give a uniform solution while stirring at room temperature. Next, refluxing was carried out for 7 hours. After leaving to cool to room temperature, the reaction liquid was diluted with 150 ml of ether, and washing performed with 100 ml of water and 200 ml of saturated aqueous $NaHCO_3$ solution. The ether layer was dried with anhydrous magnesium sulphate, and the solvent distilled off under reduced pressure. The yellow oily material obtained was purified by silica gel column chromatography (n-hexane : AcOEt = 20 : 1) and 12.6 g of the anti-form of the target compound (63% yield) and 2.98 g of the syn-form (14.8% yield) were obtained as pale yellow oily materials.

(2) Production of optical isomer of 1-[3-(methoxymethoxy)phenyl]-2-(2-naphthyl)ethylamine

Under a current of argon, 80 ml of a THF solution of 24.8 g of (-)-norephedrine was cooled to -40°C in a dry ice/acetone bath, and then 330 ml of a 1.0M THF solution of borane added dropwise over 30 minutes and stirring performed for 30 minutes. After returning the reaction liquid to room temperature, stirring was conducted for another 2 hours. Next, 80 ml of a THF solution of 11 g of the anti-isomer of the 3-(methoxymethoxy)phenyl 2-naphthylmethyl ketone-oxime O-methyl ether was added dropwise, and stirring carried out overnight. While ice-cooling, the pH was adjusted to 1 by the addition of 10% hydrochloric acid to the reaction liquid, and the solvent distilled off under reduced pressure. Then, while ice-cooling, the reaction liquid was made alkaline by the addition of 10% aqueous NaOH, after which extraction was conducted with ether (100 ml × 3). After drying the ether layer with anhydrous magnesium sulphate, the solvent was removed under reduced pressure. 25 ml of a dry THF solution of the residue obtained was added dropwise under a flow of argon to 15 ml of a THF suspension of 1.25 g of lithium aluminium hydride (LAH), and refluxing carried out for 1 hour. The reaction liquid was ice-cooled, then 2.1 ml of water, 2.9 ml of aqueous 10% NaOH solution and 5.6 ml of water were added in turn. After filtering off the insoluble matter, the solvent was distilled off under reduced pressure. Ethyl acetate was added to the residue obtained and, after drying with anhydrous magnesium sulphate, the solvent was distilled off under reduced pressure. The residue obtained was purified by silica gel column chromatography ($CHCl_3$ : MeOH = 30 : 1) and 6.51 g of

the target compound obtained as a pale yellow oily material (yield 65%).

Reference Example 7

(±)-N-allyl-2-(4-ethoxycarbonylphenyl)-1-(3-methoxymethoxyphenyl)ethylamine

225 mg of allylamine was added to 10 ml of a methanol solution of 650 mg of 3-methoxymethoxyphenyl 4-ethoxycarbonylbenzyl ketone, and 265 mg of 95% sodium cyanoborohydride added while stirring at room temperature. Next, 0.2 ml of formic acid was added dropwise, and heating and stirring carried out for 5 hours at 50°C. Following the end of the reaction, the reaction liquid was concentrated to below half under reduced pressure, then the pH adjusted to 8 by the addition of 10 ml of saturated aqueous $NaHCO_3$ solution and extraction performed with ethyl acetate (10 ml × 3). After drying with anhydrous $MgSO_4$, the solvent was distilled off under reduced pressure. The yellow oily material obtained was purified by silica gel column chromatography ($CHCl_3$ : MeOH = 50 : 1) and 360 mg of the target compound obtained as a yellow oily material.

Reference Example 8

(±)-N,N-diallyl-2-(4-ethoxycarbonylphenyl)-1-(3-methoxymethoxyphenyl)ethylamine

After adding 890 mg of (±)-N-allyl-1-(3-methoxymethoxyphenyl)-2-(4-ethoxycarbonylphenyl)ethylamine and 999 mg of potassium carbonate to 5.0 ml of N,N-dimethylformamide,

0.23 ml of allyl bromide was added dropwise at room temperature, and then heating and stirring carried out for 1 hour at 60°C. After filtering the reaction mixture, the solvent was distilled off from the filtrate. The yellow oily material obtained was purified by silica gel column chromatography (n-hexane : ethyl acetate = 9 : 1) and 800 mg of the target compound obtained as a yellow oily material.

Example 1

(±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(4-methoxyphenyl)-ethylamine hydrochloride

(1) (±)-N,N-dimethyl-1-[3-(methoxymethoxy)phenyl]-2-(4-methoxyphenyl)ethylamine

160 ml of an acetonitrile solution of 12.0 g of the (±)-1-[3-(methoxymethoxy)phenyl]-2-(4-methoxyphenyl)ethylamine obtained in Reference Example 1 was stirred at room temperature, then 35.9 g of aqueous 35% formaldehyde solution added followed by 8.3 g of sodium cyanoborohydride, after which 4.2 ml of acetic acid was added dropwise. After stirring for 30 minutes, 200 ml of a 5% aqueous sodium hydroxide solution was added and extraction with ether carried out. The ether layer was washed with water and with saturated salt solution, and then dried with anhydrous magnesium sulphate, after which the solvent was distilled off. The residue was purified by silica gel column chromatography, and 11.2 g of colourless oily target material obtained (85%).

(Alternative Method) 2.4 g of a 35% aqueous formaldehyde solution and 1.3 g of formic acid were added to 2.04 g of the (±)-1-[3-(methoxymethoxy)phenyl]-2-(4-methoxyphenyl)-ethylamine obtained in Reference Example 1, and then stirring and heating conducted for 2 hours at 50°C. After cooling, the reaction liquid was made alkaline with saturated aqueous sodium bicarbonate solution, and extraction performed with ethyl acetate (50 ml × 3). The ethyl acetate layer was washed with water and then dried with anhydrous magnesium sulphate, after which the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography, and 1.27 g of the colourless oily target material obtained.

(2) (±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(4-methoxyphenyl)ethylamine

6.0 ml of concentrated hydrochloric acid was added to 30 ml of a methanol solution of 3.15 g of (±)-N,N-dimethyl-1-[3-(methoxymethoxy)phenyl]-2-(4-methoxyphenyl)ethylamine, and stirring conducted at room temperature for 2 hours. After adding water and saturated aqueous sodium bicarbonate solution to the reaction liquid, extraction was performed with ethyl acetate. The ethyl acetate layer was washed with water and saturated salt solution, then dried with anhydrous magnesium sulphate, after which the solvent was distilled off and 2.31 g (85%) of colourless crystals of the target material obtained.

(3) (±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(4-methoxyphenyl)ethylamine hydrochloride

1.50 g of the (±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(4-methoxyphenyl)ethylamine was suspended in 15 ml of ether, then 22% HCl-MeOH added and stirring carried out for 10 minutes. The crystals which precipitated were filtered off, washed with ether and then dried under vacuum, and 1.63 g (96%) of the target compound obtained as colourless crystals.

mp 134-142°C (decomposes)

IR ($cm^{-1}$, KBr): 3150, 1613, 1516, 1246

Elemental analysis: $C_{17}H_{21}NO_2.HCl$

theoretical (%): C = 66.33, H = 7.20, N = 4.55

measured (%): C = 66.30, H = 7.42, N = 4.60

Example 2

(+)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(4-methoxyphenyl)-ethylamine hydrochloride and (-)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(4-methoxyphenyl)ethylamine hydrochloride

The compound obtained in Example 1(2) was subjected to optical resolution by separation chiral HPLC (Chiralcel OD column, n-hexane : 2-propanol : diethylamine = 95 : 5 : 0.1), and then the hydrochlorides formed in the same way as in Example 1(3). In this way the target material (+) and (-) isomers were obtained.

(+) isomer mp 191-194°C

$[\alpha]_D$ : +115.95° (c = 1.009)

Elemental analysis: $C_{17}H_{21}NO_2.HCl.1/4H_2O$

theoretical (%): C = 65.38, H = 7.26, N = 4.48

measured (%): C = 65.66, H = 7.28, N = 4.63

(-) isomer mp 197°C

$[\alpha]_D$ : -132.28° (c = 1.022)

Elemental analysis: $C_{17}H_{21}NO_2.HCl$

theoretical (%): C = 66.33, H = 7.20, N = 4.55

measured (%): C = 65.91, H = 7.21, N = 4.60

The compounds in Examples 3 to 5 below were synthesised in the same way as in Example 1.

Example 3

Asymmetric synthesis of (+)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(4-methoxyphenyl)ethylamine hydrochloride

By the same method as in Example 1, the optical isomer of 1-[3-(methoxymethoxy)phenyl]-2-(4-methoxyphenyl)ethylamine obtained in Reference Example 5 was subjected to reductive alkylation and, at the same time, removal of the protective group. The target material was obtained as the hydrochloride.

The optical purity was measured in the form of the free base by chiral HPLC (Chiralcel OD column, n-hexane : 2-propanol = 90 : 10), and was 83.4% ee.

Example 4

(±)-N,N-dimethyl-2-(4-tert-butylphenyl)-1-(3-hydroxyphenyl)-ethylamine hydrochloride

mp 230-233°C

IR ($cm^{-1}$, KBr): 3080, 1592, 1281, 1242

Elemental analysis: $C_{20}H_{27}NO.HCl.1/4H_2O$

theoretical (%): C = 70.99, H = 8.49, N = 4.14

measured (%): C = 71.34, H = 8.51, N = 4.35

Example 5

(±)-N,N-dimethyl-2-(4-ethoxyphenyl)-1-(3-hydroxyphenyl)-ethylamine hydrochloride

mp 160-162°C

IR ($cm^{-1}$, KBr): 3200, 1615, 1593, 1514, 1248

Elemental analysis: $C_{18}H_{23}NO_2.HCl$

theoretical (%): C = 66.25, H = 7.57, N = 4.29

measured (%): C = 66.49, H = 7.59, N = 4.58

The compounds in Examples 6 to 52 were synthesised in the same way as in Example 1, using the compounds obtained in Reference Example 3.

Example 6

(±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(2-naphthyl)ethyl-amine hydrochloride

colourless crystals mp: 206-208°C

IR (KBr, $cm^{-1}$): 3193, 2674, 1593, 1485, 1279, 787, 702

Elemental analysis: $C_{20}H_{21}NO.HCl$

theoretical (%): C = 73.27, H = 6.76, N = 4.27

measured (%): C = 73.23, H = 6.79, N = 4.41

Example 7

(-)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(2-naphthyl)ethylamine hydrochloride and (+)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(2-naphthyl)ethylamine hydrochloride

The compound obtained in Example 6 was subjected to optical resolution by separation chiral HPLC (Chiralcel OD column, n-hexane : 2-propanol : diethylamine = 90 : 10 : 0.1), then the hydrochlorides produced in the same way as in Example 1(3), and the (+)- and (-)-isomers obtained.

(+)-isomer

mp: 175-177°C

IR (KBr, $cm^{-1}$): 3240, 2678, 1593, 1483, 1281, 904, 818, 787, 750, 702, 478

Elemental analysis: $C_{20}H_{21}NO.HCl$

theoretical (%): C = 73.27, H = 6.76, N = 4.27

measured (%): C = 72.27, H = 6.77, N = 4.31

$[\alpha]_D$: +114.77° (c = 0.521, methanol)

(-)-isomer

mp: 183-185°C

IR (KBr, $cm^{-1}$): 3240, 2678, 1593, 1483, 1281, 904, 818, 787, 750, 702, 478

Elemental analysis: $C_{20}H_{21}NO.HCl$

theoretical (%): C = 73.27, H = 6.76, N = 4.27

measured (%): C = 72.74, H = 6.76, N = 4.31

$[\alpha]_D$: -132.66° (c = 0.502, methanol)

Example 8

Synthesis (asymmetric synthesis) of (-)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(2-naphthyl)ethylamine hydrochloride

(1) Optical isomer of N,N-dimethyl-1-[3-(methoxymethoxy)phenyl]-2-(2-naphthyl)ethylamine

Using 6.51 g of the optical isomer of 1-[3-(methoxymethoxy)phenyl]-2-(2-naphthyl)ethylamine produced in Reference Example 6, there was obtained 4.55 g of the target compound as a pale yellow oily material (yield 64%), in the same way as in Example 1.

(2) N,N-dimethyl-1-(3-hydroxyphenyl)-2-(2-naphthyl)ethylamine hydrochloride

8 ml of 22% HCl-EtOH was added to 10 ml of an ethanol solution of 4.55 g of the N,N-dimethyl-1-[3-(methoxymethoxy)phenyl]-2-(2-naphthyl)ethylamine optical isomer, and stirring carried out for 1 hour at room temperature. The reaction liquid was then poured into water and washed with ethyl acetate. The pH of the aqueous layer was adjusted to 8 by the addition of 30 ml of saturated aqueous $NaHCO_3$ solution and extraction performed with ethyl acetate (40 ml × 3). After drying with anhydrous magnesium sulphate, filtering was conducted and then the solvent distilled off under reduced pressure. 3.69 g of colourless crystals were obtained (yield 93%). Next, these crystals were recrystallized from isopropanol, and 2.77 g of colourless crystals obtained as first crystals (98%ee). Further, the filtrate was distilled under reduced pressure and recrystallization carried out from isopropanol. 0.19 g of colourless crystals were obtained as second crystals. Finally, 2.77 g of the first crystals were converted to the hydrochloride with 21% HCl-AcOEt (20 ml) and 2.98 g of the target compound obtained in the form of colourless crystals (yield 96%).

mp: 185-187°C

IR (KBr, $cm^{-1}$): 3240, 2678, 1593, 1483, 1281, 904, 818, 787, 750, 702, 478

Elemental analysis: $C_{20}H_{21}NO.HCl$

theoretical (%): C = 73.27, H = 6.76, N = 4.27

measured (%): C = 73.19, H = 6.75, N = 4.37

$[\alpha]_D$: -130.43° (c = 0.713, methanol)

Example 9

(±)-N,N-dimethyl-2-(4-biphenyl)-1-(3-hydroxyphenyl)ethyl-amine hydrochloride

IR (KBr, $cm^{-1}$): 3186, 1590, 1460, 700

Elemental analysis: $C_{22}H_{23}NO.HCl.1/2H_2O$

theoretical (%): C = 73.42, H = 6.91, N = 3.89

measured (%): C = 73.25, H = 7.20, N = 3.85

Example 10

(±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(1-naphthyl)ethyl-amine hydrochloride

mp: 227-230°C

IR (KBr, $cm^{-1}$): 3100, 1593, 1480, 1281

Elemental analysis: $C_{20}H_{21}NO.HCl.1/4H_2O$

theoretical (%): C = 72.28, H = 6.28, N = 4.21

measured (%): C = 72.35, H = 6.77, N = 4.32

Example 11

(±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(4-isopropoxy-phenyl)ethylamine hydrochloride

mp: 96-98°C

IR (KBr, $cm^{-1}$): 3250, 1593, 1510, 1244

Elemental analysis: $C_{19}H_{25}NO.HCl.2/5H_2O$

theoretical (%): C = 66.51, H = 7.75, N = 4.08

measured (%): C = 66.54, H = 7.60, N = 4.06

Example 12

(+)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(4-isopropoxyphenyl)ethylamine hydrochloride and (-)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(4-isopropoxyphenyl)ethylamine hydrochloride

The free base in Example 11 was subjected to optical resolution by separation chiral HPLC (Chiralcel OD column, n-hexane : 2-propanol : diethylamine = 95 : 5 : 0.1), then the hydrochlorides formed, and the target compound (+) and (-) isomers obtained.

(+)-isomer mp: 96-98°C

IR (KBr, $cm^{-1}$): 3400, 1512, 1460, 1254

Elemental analysis: $C_{19}H_{25}NO.HCl.3/5H_2O$

theoretical (%): C = 65.82, H = 7.91, N = 4.04

measured (%): C = 65.94, H = 8.06, N = 4.08

$[\alpha]_D$: +208.26° (c = 0.484, $CHCl_3$)

(-)-isomer mp: 96-98°C

IR (KBr, $cm^{-1}$): 3400, 1512, 1460, 1254

Elemental analysis: $C_{19}H_{25}NO.HCl.1/2H_2O$

theoretical (%): C = 66.16, H = 7.89, N = 4.06

measured (%): C = 66.03, H = 8.17, N = 4.08

$[\alpha]_D$: -202.25° (c = 0.709, $CHCl_3$)

Example 13

(±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(4-trifluoromethyl-phenyl)ethylamine hydrochloride

mp: 229-231°C

IR (KBr, $cm^{-1}$): 3181, 2681, 1593, 1371, 1323

Elemental analysis: $C_{17}H_{18}NO.HCl$

theoretical (%): C = 59.05, H = 5.54, N = 4.05

measured (%): C = 59.23, H = 5.77, N = 4.43

Example 14

(+)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(4-trifluoromethyl-phenyl)ethylamine hydrochloride and (-)-N,N-dimethyl-2-(4-trifluoromethylphenyl)-1-(3-hydroxyphenyl)ethylamine hydrochloride

The free base in Example 13 was subjected to optical resolution by separation chiral HPLC (Chiralcel AD column, n-hexane : 2-propanol : diethylamine = 95 : 5 : 0.1), then the hydrochlorides formed, and the target compound (+) and (-) isomers obtained.

(+)-isomer mp: 218-219°C

IR (KBr, $cm^{-1}$): 3181, 2681, 1593, 1327, 1161, 1130

Elemental analysis: $C_{17}H_{18}NO.HCl$

theoretical (%): C = 59.05, H = 5.54, N = 4.05

measured (%): C = 59.02, H = 5.50, N = 4.08

$[\alpha]_D$: +107.99° (c = 0.600, methanol)

(-)-isomer mp: 214-216°C

IR (KBr, $cm^{-1}$): 3181, 2681, 1593, 1327, 1161, 1130

Elemental analysis: $C_{17}H_{18}NO.HCl$

theoretical (%): C = 59.05, H = 5.54, N = 4.05

measured (%): C = 59.14, H = 5.59, N = 4.06

$[\alpha]_D$: -104.18° (c = 0.716, methanol)

Example 15

(±)-N,N-dimethyl-2-(4-N,N-diethylcarbamoylphenyl)-1-(3-hydroxyphenyl)ethylamine hydrochloride

IR (KBr, $cm^{-1}$): 3200, 2973, 1610, 1462, 1287, 791

Elemental analysis: $C_{21}H_{28}N_2O_2.HCl.H_2O$

theoretical (%): C = 63.87, H = 7.91, N = 7.09

measured (%): C = 64.09, H = 8.30, N = 7.15

Example 16

(±)-N,N-dimethyl-2-(4-carbamoylphenyl)-1-(3-hydroxyphenyl)ethylamine hydrochloride

mp: 249-252°C

IR (KBr, $cm^{-1}$): 3191, 1661, 1456, 1271

Elemental analysis: $C_{17}H_{20}N_2O_2.HCl.1/3H_2O$

theoretical (%): C = 62.48, H = 6.68, N = 8.57

measured (%): C = 62.37, H = 6.58, N = 8.60

Example 17

(±)-N,N-dimethyl-2-(4-N,N-dimethylcarbamoylphenyl)-1-(3-hydroxyphenyl)ethylamine hydrochloride

IR (KBr, $cm^{-1}$): 3200, 1614, 1460, 1086, 790

Elemental analysis: $C_{19}H_{24}N_2O_2.HCl.H_2O$

theoretical (%): C = 62.20, H = 7.41, N = 7.64

measured (%): C = 62.26, H = 7.31, N = 7.43

Example 18

(+)-N,N-dimethyl-2-(4-N,N-dimethylcarbamoylphenyl)-1-(3-hydroxyphenyl)ethylamine hydrochloride

The free base of the compound in Example 17 was subjected to optical resolution by separation chiral HPLC (Chiralcel OD column, n-hexane : 2-propanol : diethylamine = 90 : 10 : 0.1), then the hydrochlorides formed, and the target compound (+) and (-) isomers obtained.

(+)-isomer mp: 112-114°C

IR (KBr, $cm^{-1}$): 1617, 1489, 1458

Elemental analysis: $C_{19}H_{24}N_2O_2.HCl.2/5H_2O$

theoretical (%): C = 64.09, H = 7.30, N = 7.87

measured (%): C = 64.08, H = 7.58, N = 7.55

$[\alpha]^{20}_D$: 94.38° (c = 1.087, methanol)

(-)-isomer mp: 127-129°C

IR (KBr, $cm^{-1}$): 1617, 1489, 1458

Elemental analysis: $C_{19}H_{24}N_2O_2.HCl.2/5H_2O$

theoretical (%): C = 64.09, H = 7.30, N = 7.87

measured (%): C = 63.91, H = 7.13, N = 8.03

$[\alpha]^{20}_D$: -106.41° (c = 1.060, methanol)

Example 19

(±)-N,N-dimethyl-2-(4-N-ethylcarbamoylphenyl)-1-(3-hydroxyphenyl)ethylamine hydrochloride

mp: 220-225°C

IR (KBr, $cm^{-1}$): 3250, 1634, 1545, 1462, 1282

Elemental analysis: $C_{19}H_{24}N_2O_2.HCl.H_2O$

theoretical (%): C = 62.20, H = 7.42, N = 7.64

measured (%): C = 62.49, H = 7.46, N = 7.91

Example 20

(±)-N,N-dimethyl-2-(4-N-benzylcarbamoylphenyl)-1-(3-hydroxyphenyl)ethylamine hydrochloride

mp: 149-152°C

IR (KBr, $cm^{-1}$): 3250, 1638, 1543, 1456, 1283, 702

Elemental analysis: $C_{24}H_{26}N_2O_2.HCl.2/3H_2O$

theoretical (%): C = 68.16, H = 6.75, N = 6.62

measured (%): C = 68.28, H = 7.03, N = 6.59

Example 21

(±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(4-N-phenethyl-carbamoylphenyl)ethylamine hydrochloride

mp: 143-147°C

IR (KBr, $cm^{-1}$): 3250, 1638, 1545, 1499, 1456, 1314, 1283, 702

Elemental analysis: $C_{25}H_{28}N_2O_2.HCl.1/5H_2O$

theoretical (%): C = 70.06, H = 6.91, N = 6.54

measured (%): C = 69.98, H = 7.09, N = 6.65

Example 22

(±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(4-pyrrolidino-carbonoylphenyl)ethylamine hydrochloride

mp: 148-153°C

IR (KBr, $cm^{-1}$): 3200, 1605, 1445, 1281, 1242

Elemental analysis: $C_{21}H_{26}N_2O_2.HCl.3/2H_2O$

theoretical (%): C = 62.75, H = 7.52, N = 6.97

measured (%): C = 62.82, H = 7.51, N = 6.94

Example 23

(±)-N,N-dimethyl-2-(4-ethoxycarbonylphenyl)-1-(3-hydroxyphenyl)ethylamine hydrochloride

Synthesis was carried out in the same way as in Example 1, using compound 12 from Reference Example 3.

mp: 201-204°C

Elemental analysis: $C_{19}H_{23}NO_3.HCl$

theoretical (%): C = 65.23, H = 6.91, N = 4.00

measured (%): C = 64.95, H = 6.90, N = 4.07

Example 24

(+)-N,N-dimethyl-2-(4-ethoxycarbonylphenyl)-1-(3-hydroxyphenyl)ethylamine hydrochloride and (-)-N,N-dimethyl-2-(4-ethoxycarbonylphenyl)-1-(3-hydroxyphenyl)ethylamine hydrochloride

The free base in Example 23 was subjected to optical resolution by separation chiral HPLC (Chiralcel OD column, n-hexane : 2-propanol : diethylamine = 90 : 10 : 0.1), then the hydrochlorides formed, and the target compound (+) and (-) isomers obtained.

(+)-isomer mp: 233-235°C

IR (KBr, $cm^{-1}$): 3158, 1713, 1279, 1102

Elemental analysis: $C_{19}H_{23}NO_3.HCl$

theoretical (%): C = 65.23, H = 6.91, N = 4.00

measured (%): C = 64.95, H = 6.95, N = 3.98

$[\alpha]_D$: +117.93° (c = 0.524, methanol)

(-)-isomer mp: 235-236°C

IR (KBr, $cm^{-1}$): 3158, 1703, 1283, 1105

Elemental analysis: $C_{19}H_{23}NO_3.HCl$

theoretical (%): C = 65.23, H = 6.91, N = 4.00

measured (%): C = 65.14, H = 6.88, N = 3.88

$[\alpha]_D$: -131.48° (c = 0.613, methanol)

Example 25

(-)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(4-methoxycarbonoyl-phenyl)ethylamine hydrochloride

IR (KBr, $cm^{-1}$): 3164, 1707, 1289

Elemental analysis: $C_{18}H_{21}NO_3.HCl$

theoretical (%): C = 64.38, H = 6.60, N = 4.17

measured (%): C = 64.25, H = 6.76, N = 4.26

Example 26

(-)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(4-isopropoxy-carbonoylphenyl)ethylamine hydrochloride

IR (KBr, $cm^{-1}$): 3160, 1700, 1285

Elemental analysis: $C_{20}H_{25}NO_3.HCl$

theoretical (%): C = 66.02, H = 7.20, N = 3.85

measured (%): C = 65.68, H = 7.18, N = 4.16

Example 27

(±)-N,N-dimethyl-2-[4-(2-fluoroethoxycarbonyl)phenyl]-1-(3-hydroxyphenyl)ethylamine hydrochloride

mp: 203-205°C

IR (KBr, $cm^{-1}$): 3154, 1709, 1285

Elemental analysis: $C_{19}H_{22}FNO_3.HCl$

theoretical (%): C = 62.04, H = 6.30, N = 3.81

measured (%): C = 62.59, H = 6.49, N = 3.94

Example 28

(±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-[4-(2,2,2-trifluoroethoxycarbonyl)phenyl]ethylamine hydrochloride

IR (KBr, $cm^{-1}$): 3164, 1738, 1289, 1175, 1102

Elemental analysis: $C_{19}H_{20}F_3NO_3.HCl$

theoretical (%): C = 56.51, H = 5.24, N = 3.47

measured (%): C = 56.70, H = 4.99, N = 3.64

Example 29

(±)-N,N-dimethylamino-1-(3-hydroxyphenyl)-2-(phthalid-5-yl)ethylamine hydrochloride

IR (KBr, $cm^{-1}$): 2946, 1763, 1584, 1483, 1279, 1046, 1005

Elemental analysis: $C_{18}H_{19}NO_3.HCl.3/2H_2O$

theoretical (%): C = 59.92, H = 6.42, N = 3.88

measured (%): C = 59.92, H = 6.15, N = 3.91

Example 30

(±)-N,N-dimethyl-2-(3-ethoxycarbonylphenyl)-1-(3-hydroxyphenyl)ethylamine hydrochloride

mp: 202-205°C

IR (KBr, $cm^{-1}$): 3180, 1717, 1590, 1283

Elemental analysis: $C_{19}H_{23}NO_3.HCl.1/4H_2O$

theoretical (%): C = 64.44, H = 6.97, N = 3.95

measured (%): C = 64.52, H = 6.95, N = 3.99

Example 31

(±)-N,N-dimethyl-2-(4-ethoxycarbonylmethylphenyl)-1-(3-hydroxyphenyl)ethylamine hydrochloride

IR (KBr, $cm^{-1}$): 1730, 1592, 1281, 1229

Elemental analysis: $C_{20}H_{25}NO_3.HCl.1/2H_2O$

theoretical (%): C = 64.42, H = 7.30, N = 3.76

measured (%): C = 64.24, H = 7.28, N = 3.99

Example 32

(±)-N,N-dimethyl-2-(4-cyanophenyl)-1-(3-hydroxyphenyl)-ethylamine hydrochloride

IR (KBr, $cm^{-1}$): 3250, 2230, 1458, 1281

Elemental analysis: $C_{17}H_{18}N_2O.HCl.9/5H_2O$

theoretical (%): C = 60.91, H = 6.80, N = 8.36

measured (%): C = 60.85, H = 6.69, N = 8.42

Example 33

(±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(4-methylthiophenyl)-ethylamine hydrochloride

IR (KBr, $cm^{-1}$): 3180, 1603, 1589, 1460, 787

Elemental analysis: $C_{17}H_{21}NOS.HCl.8/9H_2O$

theoretical (%): C = 60.07, H = 7.05, N = 4.12

measured (%): C = 60.07, H = 7.25, N = 4.10

Example 34

(±)-N,N-dimethyl-2-(benzofuran-2-yl)-1-(3-hydroxyphenyl)-ethylamine hydrochloride

mp: 152-156°C

IR (KBr, $cm^{-1}$): 3190, 2664, 1595, 1454, 1280

Elemental analysis: $C_{18}H_{19}NO_2.HCl$

theoretical (%): C = 68.03, H = 6.34, N = 4.41

measured (%): C = 68.15, H = 6.31, N = 4.35

Example 35

(±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(6-methoxy-2-naphthyl)ethylamine hydrochloride

mp: 189-190°C (decomposes)

IR (KBr, $cm^{-1}$): 3250, 2683, 1606, 1591, 1485, 1265, 1228

Elemental analysis: $C_{21}H_{23}NO_2.HCl.1/2H_2O$

theoretical (%): C = 68.75, H = 6.86, N = 3.82

measured (%): C = 69.02, H = 7.16, N = 3.84

Example 36

(±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(2-methylbenzofuran-5-yl)ethylamine hydrochloride

IR (KBr, $cm^{-1}$): 2465, 1591, 1473, 1259, 792

Elemental analysis: $C_{19}H_{21}NO_2.HCl.H_2O$

theoretical (%): C = 65.29, H = 6.91, N = 4.00

measured (%): C = 65.84, H = 7.27, N = 3.77

Example 37

(±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(5-methoxybenzofuran-2-yl)ethylamine hydrochloride

IR (KBr, $cm^{-1}$): 2681, 1603, 1477, 1205, 792

Elemental analysis: $C_{19}H_{21}NO_3.HCl.3/4H_2O$

theoretical (%): C = 63.15, H = 6.55, N = 3.88

measured (%): C = 63.01, H = 6.59, N = 3.83

Example 38

(±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(3-trifluoromethyl-phenyl)ethylamine hydrochloride

IR (KBr, $cm^{-1}$): 3200, 1591, 1460, 1333, 1122, 702

Elemental analysis: $C_{17}H_{18}F_3NO.HCl.1/2H_2O$

theoretical (%): C = 57.55, H = 5.68, N = 3.94

measured (%): C = 57.42, H = 6.01, N = 3.85

Example 39

(±)-N,N-dimethyl-2-(1-fluoro-2-naphthyl)-1-(3-hydroxy-phenyl)ethylamine hydrochloride

mp: 236-238°C

IR (KBr, $cm^{-1}$): 3200, 2700, 1598, 1485, 1381, 1281

Elemental analysis: $C_{20}H_{20}FNO.9/5HCl$

theoretical (%): C = 67.47, H = 6.17, N = 3.93

measured (%): C = 67.71, H = 6.00, N = 4.16

Example 40

(±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(3-quinolyl)ethyl-amine hydrochloride

IR (KBr, $cm^{-1}$): 3250, 2430, 1589, 1512, 1464, 1117, 789

Elemental analysis: $C_{19}H_{20}N_2O.HCl.3/2H_2O$

theoretical (%): C = 58.17, H = 6.42, N = 7.14

measured (%): C = 57.56, H = 6.77, N = 9.81

Example 41

(±)-N,N-dimethyl-2-(benzofuran-6-yl)-1-(3-hydroxyphenyl)-ethylamine hydrochloride

mp: 211-214°C

IR (KBr, $cm^{-1}$): 3150, 2658, 1589, 1433, 1263

Elemental analysis: $C_{18}H_{19}NO_2.HCl$

theoretical (%): C = 68.03, H = 6.34, N = 4.01

measured (%): C = 67.46, H = 6.50, N = 4.22

Example 42

(+)-N,N-dimethyl-2-(benzofuran-6-yl)-1-(3-hydroxyphenyl)-ethylamine hydrochloride and (-)-N,N-dimethyl-2-(benzofuran-6-yl)-1-(3-hydroxyphenyl)ethylamine hydrochloride

The free base in Example 41 was subjected to optical resolution by separation chiral HPLC (Chiralcel OD column, n-hexane : 2-propanol : diethylamine = 95 : 5 : 0.1), then the hydrochlorides formed, and the target compound (+) and (-) isomers obtained.

(+)-isomer mp: 241-243°C

IR (KBr, $cm^{-1}$): 3154, 2672, 1590, 1474, 1316

Elemental analysis: $C_{18}H_{19}NO_2.HCl.5/12H_2O$

theoretical (%): C = 66.45, H = 6.45, N = 4.31

measured (%): C = 66.42, H = 6.28, N = 4.28

$[\alpha]_D$: +227.11° (c = 0.295, methanol)

(-)-isomer mp: 241-243°C

IR (KBr, $cm^{-1}$): 3154, 2672, 1590, 1474, 1316

Elemental analysis: $C_{18}H_{19}NO_2.HCl.1/5H_2O$

theoretical (%): C = 67.26, H = 6.40, N = 4.36

measured (%): C = 67.15, H = 6.33, N = 4.40

$[\alpha]_D$: -245.26° (c = 0.380, methanol)

Example 43

(±)-N,N-dimethyl-2-(8-fluoro-2-naphthyl)-1-(3-hydroxyphenyl)ethylamine hydrochloride

Synthesis was conducted in the same way as in Example 1, using Compound 30 in Reference Example 3.

mp: 227-227.5°C

IR (KBr, $cm^{-1}$): 3193, 2680, 1605, 1586, 1479, 1321, 1266, 1237, 1198, 1038, 1017, 945, 830, 799, 749

Elemental analysis: $C_{20}H_{20}FNO.HCl.1/4H_2O$

theoretical (%): C = 68.57, H = 6.19, N = 4.00

measured (%): C = 68.69, H = 6.20, N = 3.99

Example 44

(+)-N,N-dimethyl-2-(8-fluoro-2-naphthyl)-1-(3-hydroxyphenyl)ethylamine hydrochloride and (-)-N,N-dimethyl-2-(8-fluoro-2-naphthyl)-1-(3-hydroxyphenyl)ethylamine hydrochloride

The free base in Example 43 was subjected to optical resolution by separation chiral HPLC (Chiralcel OD column, n-hexane : 2-propanol : diethylamine = 95 : 5 : 0.1), then the hydrochlorides formed, and the target compound (+) and (-) isomers obtained.

(+)-isomer mp: 217-219°C (ethyl acetate)

IR (KBr, $cm^{-1}$): 3139, 2640, 1609, 1590, 1475, 1312, 1034, 936, 830, 783, 702

Elemental analysis: $C_{20}H_{20}FNO.HCl.1/4H_2O$

theoretical (%): C = 68.57, H = 6.19, N = 4.00

measured (%): C = 68.63, H = 5.96, N = 4.00

$[\alpha]_D$: +131.04° (c = 0.496, methanol)

(-)-isomer mp: 217-219°C (ethyl acetate)

IR (KBr, $cm^{-1}$): 3139, 2640, 1609, 1590, 1475, 1312, 1034, 936, 830, 783, 702

Elemental analysis: $C_{20}H_{20}FNO.HCl.1/4H_2O$

theoretical (%): C = 68.57, H = 6.19, N = 4.00

measured (%): C = 68.72, H = 6.03, N = 4.02

$[\alpha]_D$: -132.30° (c = 0.582, methanol)

Example 45

(±)-N,N-dimethyl-2-(4-ethoxymethylphenyl)-1-(3-hydroxyphenyl)ethylamine hydrochloride

IR (KBr, $cm^{-1}$): 2973, 1592, 1458, 1281, 1098

Elemental analysis: $C_{19}H_{25}NO_2.HCl.1/2H_2O$

theoretical (%): C = 66.17, H = 7.89, N = 4.06

measured (%): C = 66.17, H = 7.81, N = 4.28

Synthesis was carried out in the same way as in Example 1 using Compound 31 in Reference Example 3.

Example 46

(+)-N,N-dimethyl-2-(4-ethoxymethylphenyl)-1-(3-hydroxyphenyl)ethylamine hydrochloride and (-)-N,N-dimethyl-2-(4-ethoxymethylphenyl)-1-(3-hydroxyphenyl)ethylamine hydrochloride

The free base in Example 45 was subjected to optical resolution by separation chiral HPLC (Chiralcel OD column, n-hexane : 2-propanol : diethylamine = 95 : 5 : 0.1), then the hydrochlorides formed, and the target compound (+) and (-) isomers obtained.

(+)-isomer IR (KBr, $cm^{-1}$): 3200, 1591, 1458, 1281, 1098

Elemental analysis: $C_{19}H_{25}NO_2.HCl.3/2H_2O$

theoretical (%): C = 65.60, H = 7.91, N = 4.03

measured (%): C = 65.80, H = 7.91, N = 4.21

$[\alpha]^{20}_D$: 106.59° (c = 0.394, methanol)

(-)-isomer IR (KBr, $cm^{-1}$): 3200, 1591, 1460, 1281, 1098

Elemental analysis: $C_{19}H_{25}NO_2.HCl.1/2H_2O$

theoretical (%): C = 66.17, H = 7.89, N = 4.06

measured (%): C = 66.05, H = 7.97, N = 4.23

$[\alpha]^{20}_D$: -106.38° (c = 0.752, methanol)

Example 47

(+)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(4-methoxymethyl-phenyl)ethylamine hydrochloride

mp: 158-159°C

IR (KBr, $cm^{-1}$): 3200, 2679, 1592, 1483, 1279, 1092

Elemental analysis: $C_{18}H_{23}NO_2.HCl$

theoretical (%): C = 67.17, H = 7.52, N = 4.35

measured (%): C = 67.05, H = 7.68, N = 4.39

$[\alpha]^{20}_D$: 101.61° (c = 0.620, methanol)

Example 48

(±)-N,N-dimethyl-2-[4-(2-fluoroethoxymethyl)phenyl]-1-(3-hydroxyphenyl)ethylamine hydrochloride

IR (KBr, $cm^{-1}$): 3195, 1588, 1458

Elemental analysis: $C_{19}H_{24}FNO_2.HCl.1/2H_2O$

theoretical (%): C = 69.86, H = 6.45, N = 4.07

measured (%): C = 69.71, H = 6.61, N = 3.94

Example 49

(±)-N,N-dimethyl-2-(2,4-dichlorophenyl)-1-(3-hydroxyphenyl)-ethylamine hydrochloride

mp: 220-222°C

IR (KBr, $cm^{-1}$): 3098, 1593, 1473, 1237

Elemental analysis: $C_{16}H_{17}Cl_2NO.HCl$

theoretical (%): C = 54.72, H = 5.31, N = 3.99

measured (%): C = 54.78, H = 5.30, N = 3.99

Example 50

(±)-N,N-dimethyl-2-(3,4-dichlorophenyl)-1-(3-hydroxyphenyl)-ethylamine hydrochloride

mp: 178-179°C

IR (KBr, $cm^{-1}$): 3200, 1591, 1474, 1287, 791

Elemental analysis: $C_{16}H_{17}Cl_2NO.HCl.1/5H_2O$

theoretical (%): C = 54.86, H = 5.29, N = 4.00

measured (%): C = 54.74, H = 5.38, N = 3.99

Example 51

(±)-N,N-dimethyl-2-(benzofuran-5-yl)-1-(3-hydroxyphenyl)-ethylamine hydrochloride

mp: 188-190°C (ethyl acetate/ether)

IR (KBr, $cm^{-1}$): 3200, 1990, 1470, 1264

Elemental analysis: $C_{18}H_{19}FNO_2.HCl.1/2H_2O$ *{sic}*

theoretical (%): C = 66.15, H = 6.48, N = 4.29

measured (%): C = 65.90, H = 6.75, N = 4.57

Example 52

(±)-N,N-dimethyl-2-(4-N,N-dimethylsulphonylphenyl[ii])-1-(3-hydroxyphenyl)ethylamine hydrochloride

mp: 172-177°C

IR (KBr, $cm^{-1}$): 3400, 2691, 1337, 1167

Elemental analysis: $C_{18}H_{24}N_2O_3S.HCl.1/3H_2O$

theoretical (%): C = 55.30, H = 6.62, N = 7.17

measured (%): C = 55.29, H = 6.80, N = 7.18

Example 53

(±)-N,N-dimethyl-2-(4-carboxyphenyl)-1-(3-hydroxyphenyl)-ethylamine hydrochloride

(1) 5.9 g of the (±)-N,N-dimethyl-2-(4-ethoxycarbonylphenyl)-1-(3-methoxymethoxyphenyl)ethylamine obtained in Example 23 was dissolved in 50 ml of methanol, then 10 ml of an aqueous 10% sodium hydroxide solution added, and the reaction mixture heated and refluxed through the night. After distilling off the methanol, the pH was adjusted to 4-5 with 10% aqueous citric acid solution, and then extraction carried out with ethyl acetate (20 ml × 15). After drying with anhydrous magnesium sulphate, the solvent was distilled off, and (±)-N,N-dimethyl-2-(4-carboxyphenyl)-1-(3-methoxymethoxyphenyl)ethylamine (4.5 g) obtained as a colourless solid.

(2) By subjecting the compound obtained in (1) to the same procedure as in Example 1 (2) and (3), the target compound was obtained.

IR (KBr, $cm^{-1}$): 2463, 1612, 1462, 1279, 1111

Elemental analysis: $C_{17}H_{19}NO_3.HCl.2H_2O$

theoretical (%): C = 57.06, H = 6.76, N = 3.91

measured (%): C = 57.41, H = 6.65, N = 4.04

Example 54

(±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(4-N-methoxy-N-methylcarbamoylphenyl)ethylamine hydrochloride

(1) 1.3 ml of triethylamine was added dropwise, at room temperature and while stirring, to a mixture of 2.6 g of the (±)-N,N-dimethyl-2-(4-carboxyphenyl)-1-(3-methoxymethoxyphenyl)ethylamine obtained in Example 53, 923 mg of

N-methoxy-N-methylamine hydrochloride and 25 ml of N,N-dimethylformamide, and then the stirring continued for 15 minutes. While ice-cooling, 1.5 g of 93% diethyl cyanophosphonate was added dropwise, after which 1.2 ml of triethylamine was added dropwise and stirring carried out for 30 minutes. After further stirring throughout the night at room temperature, the reaction mixture was poured into 50 ml of ice water, and then extraction performed with ethyl acetate. After washing with a small amount of saturated salt solution, drying was conducted with anhydrous magnesium sulphate and the solvent distilled off. The brown-coloured oily material obtained was purified by silica gel column chromatography ($CHCl_3$ : MeOH = 100 : 1), and 2.4 g of (±)-N,N-dimethyl-1-(3-methoxymethoxyphenyl)-2-(4-N-methoxy-N-methylcarbamoylphenyl)ethylamine obtained as a colourless oily material.

(2) The target compound was obtained from this in the same way as in Example 1 (2) and (3).

IR (KBr, $cm^{-1}$): 3200, 1615, 1460, 1280, 999

Elemental analysis: $C_{19}H_{24}N_2O_3.HCl.1/2H_2O$

theoretical (%): C = 61.04, H = 7.01, N = 7.49

measured (%): C = 60.89, H = 7.17, N = 7.59

Example 55

(±)-N,N-dimethyl-2-(4-butyrylphenyl)-1-(3-hydroxyphenyl)-ethylamine hydrochloride

(1) Under a current of argon, and while ice-cooling, a THF solution of n-propylmagnesium bromide was added dropwise to a 10 ml anhydrous tetrahydrofuran solution of 372 mg of the (±)-N,N-dimethyl-1-(3-methoxymethoxyphenyl)-2-(4-N-methoxy-N-methylcarbamoylphenyl)ethylamine obtained in Example 54 (1). After stirring for 1 hour while ice-cooling, the reaction mixture was poured into 50 ml of saturated ammonium chloride solution. Extraction was conducted with ethyl acetate and, after washing with a small quantity of saturated salt solution, drying was carried out with anhydrous magnesium sulphate and then the solvent distilled off. The brown-coloured oily material obtained was purified by silica gel column chromatography ($CHCl_3$ : MeOH = 50 : 1), and (±)-N,N-dimethyl-2-(4-butyrylphenyl)-1-(3-methoxymethoxyphenyl)ethylamine obtained as a colourless oily material (317 mg)

(2) The target compound was obtained from the compound produced in (1) in the same way as in Example 1 (2) and (3).

mp: 105-107°C

IR (KBr, $cm^{-1}$): 2963, 1682, 1607, 1460, 1281, 1221

Elemental analysis: $C_{20}H_{25}NO_2.HCl.2/5H_2O$

theoretical (%): C = 67.65, H = 7.61, N = 3.94

measured (%): C = 67.89, H = 7.75, N = 4.31

Synthesis of the compounds in Examples 56 to 60 was carried out in the same way as in Example 55.

Example 56

(±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(4-vinylacetyl-phenyl)ethylamine hydrochloride

mp: 107-111°C (ethyl acetate/ether)

IR (KBr, $cm^{-1}$): 2971, 1684, 1607, 1460, 1283, 1227

Elemental analysis: $C_{20}H_{23}NO_2.HCl.5/4H_2O$

theoretical (%): C = 65.21, H = 7.25, N = 3.80

measured (%): C = 65.29, H = 7.23, N = 3.87

Example 57

(±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(4-propionylphenyl)-ethylamine hydrochloride

mp: 238-239°C

IR (KBr, $cm^{-1}$): 2941, 1674, 1586, 14485 *{sic}*, 1281, 1252, 1231

Elemental analysis: $C_{19}H_{23}NO_2.HCl.1/4H_2O$

theoretical (%): C = 67.45, H = 7.30, N = 4.14

measured (%): C = 67.34, H = 7.32, N = 4.46

Example 58

(-)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(4-isobutyryl-phenyl)ethylamine hydrochloride

IR (KBr, $cm^{-1}$): 2969, 1684, 1605, 1485, 1229

Elemental analysis: $C_{20}H_{25}NO_2.HCl.1/2H_2O$

theoretical (%): C = 67.31, H = 7.63, N = 3.92

measured (%): C = 67.47, H = 7.63, N = 4.26

Example 59

(±)-N,N-dimethyl-2-(4-acetylphenyl)-1-(3-hydroxyphenyl)-ethylamine hydrochloride

IR (KBr, $cm^{-1}$): 3250, 1680, 1607, 1271, 790

Elemental analysis: $C_{18}H_{21}NO_2.HCl$

theoretical (%): C = 65.75, H = 7.05, N = 4.25

measured (%): C = 65.93, H = 7.30, N = 4.46

Example 60

(+)-N,N-dimethyl-2-(4-acetylphenyl)-1-(3-hydroxyphenyl)-ethylamine hydrochloride and (-)-N,N-dimethyl-2-(4-acetylphenyl)-1-(3-hydroxyphenyl)ethylamine hydrochloride

The free base of the compound in Example 59 was subjected to optical resolution by separation chiral HPLC (Chiralcel OD column, n-hexane : 2-propanol : diethylamine = 90 : 10 : 0.1), and then the (+) and (-) isomers obtained as their hydrochlorides.

(+)-isomer IR (KBr, $cm^{-1}$): 3250, 1680, 1607, 1271, 790

Elemental analysis: $C_{18}H_{21}NO_2.HCl.H_2O$

theoretical (%): C = 63.99, H = 7.16, N = 4.14

measured (%): C = 63.67, H = 6.87, N = 4.38

$[\alpha]^{20}_D$: 116.93° (c = 0.431, methanol)

(-)-isomer IR (KBr, $cm^{-1}$): 3250, 1680, 1607, 1269, 790

Elemental analysis: $C_{18}H_{21}NO_2.HCl.H_2O$

theoretical (%): C = 63.99, H = 7.16, N = 4.14

measured (%): C = 63.93, H = 7.12, N = 4.12

$[\alpha]^{20}_D$: -131.20° (c = 0.439, methanol)

Example 61

(±)-N,N-dimethyl-2-(4-hydroxymethylphenyl)-1-(3-hydroxyphenyl)ethylamine hydrochloride

The target compound was produced by the reduction of the (±)-N,N-dimethyl-2-(4-ethoxycarbonylphenyl)-1-(3-hydroxyphenyl)ethylamine obtained in Example 23 using lithium aluminium hydride, and conversion of the compound obtained to the hydrochloride.

IR (KBr, $cm^{-1}$): 3250, 1277

Elemental analysis: $C_{20}H_{25}NO_2.HCl.H_2O$ *{sic}*[iii]

theoretical (%): C = 62.67, H = 7.42, N = 4.30

measured (%): C = 62.82, H = 7.37, N = 4.60

Example 62

(±)-N,N-dimethyl-2-(4-fluorophenyl)-1-(3-hydroxyphenyl)-ethylamine hydrochloride

(1) (±)-N-methyl-2-(4-fluorophenyl)-1-[3-(methoxymethoxy)-phenyl]ethylamine

A Grignard reagent prepared from 2.60 g of 4-fluorobenzyl chloride, 0.44 g of magnesium and 18 ml of dry tetrahydrofuran was stirred at room temperature in argon gas, and then 18 ml of a dry tetrahydrofuran solution of 2.20 g of the N-[3-(methoxymethoxy)benzylidene]methylamine obtained in Reference Example 4 was added dropwise, and the stirring continued overnight at room temperature. Aqueous ammonium chloride solution was added to the reaction liquid, and then extraction with ether performed. After washing with water and saturated salt solution, and then drying with anhydrous magnesium sulphate, the solvent was distilled off. The residue obtained was purified by column chromatography, and 2.02 g of a pale brown oily material obtained (yield 57%).

(2) (±)-N,N-dimethyl-2-(4-fluorophenyl)-1-[3-(methoxy-methoxy)phenyl]ethylamine

3.0 g of a 35% aqueous formaldehyde solution was added to 15 ml of an acetonitrile solution of 1.00 g of the (±)-N-methyl-2-(4-fluorophenyl)-1-[3-(methoxymethoxy)phenyl]-ethylamine, followed by 0.63 g of sodium cyanoborohydride, after which 0.35 ml of acetic acid was slowly added and stirring carried out for 2 hours. 20 ml of 5% aqueous sodium hydroxide solution was then added to the reaction liquid and extraction performed with ether. After washing with water and with saturated salt solution, and then drying with anhydrous magnesium sulphate, the solvent was

distilled off. The residue obtained was purified by silica gel column chromatography and there was obtained 0.52 g of the target compound as a pale-brown oily material (yield 50%).

(3) (±)-N,N-dimethyl-2-(4-fluorophenyl)-1-(3-hydroxyphenyl)ethylamine hydrochloride

0.47 g of the (±)-N,N-dimethyl-2-(4-fluorophenyl)-1-[3-(methoxymethoxy)phenyl]ethylamine obtained in (3) *{sic}* was subjected to protective group removal and hydrochloride formation in the same way as in Example 1, and 0.26 g of the target compound obtained.

mp 201-203°C (decomposes)

IR (KBr, $cm^{-1}$): 3100, 1619, 1588, 1510, 1217

Elemental analysis: $C_{16}H_{18}FNO.HCl$

theoretical (%): C = 64.97, H = 6.47, N = 4.74

measured (%): C = 65.73, H = 6.70, N = 4.79

The compounds in Examples 63 to 65 below were synthesised in the same way as in Example 62.

Example 63

(±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(4-phenoxyphenyl)-ethylamine hydrochloride

mp 184°C

IR (KBr, $cm^{-1}$): 3080, 1590, 1507, 1489, 1242

Elemental analysis: $C_{22}H_{23}NO_2.HCl$

theoretical (%): C = 71.44, H = 6.54, N = 3.79

measured (%): C = 70.94, H = 6.68, N = 3.74

Example 64

(±)-N,N-dimethyl-2-(4-n-butoxyphenyl)-1-(3-hydroxyphenyl)-ethylamine hydrochloride

mp 155-158°C

IR (KBr, $cm^{-1}$): 3250, 2950, 2680, 1615, 1592, 1512, 1474, 1246, 1181, 1009, 787, 698

Elemental analysis: $C_{20}H_{27}NO_2.HCl$

theoretical (%): C = 68.65, H = 8.07, N = 4.00

measured (%): C = 68.00, H = 7.97, N = 4.32

Example 65

(±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(2-quinolyl)ethyl-amine hydrochloride

IR (KBr, $cm^{-1}$): 3100, 1630, 1605, 1578, 1248, 746

Elemental analysis: $C_{19}H_{20}N_2O.2HCl.3H_2O$

theoretical (%): C = 54.42, H = 6.73, N = 6.68

measured (%): C = 54.23, H = 6.84, N = 6.64

Example 66

Synthesis of (±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(3-methoxyphenyl)ethylamine hydrochloride

(1) (±)-N,N-dimethyl-1-[3-(methoxymethoxy)phenyl]-2-(3-methoxyphenyl)ethylamine

A Grignard reagent prepared from 1.56 g of 3-methoxybenzyl chloride, 0.27 g of magnesium and 10 ml of dry ether was stirred at room temperature in argon gas, then 20 ml of a dry tetrahydrofuran solution of 1.0 g of the (±)-2-dimethylamino-2-[3-(methoxymethoxy)phenyl]acetonitrile obtained in Reference Example 2 was added dropwise, and stirring continued in the same way overnight. Aqueous ammonium chloride solution was added to the reaction liquid and then extraction with ether performed. After washing with water and saturated salt solution, and then drying with anhydrous magnesium sulphate, the solvent was distilled off. The residue was purified by silica gel column chromatography, and 0.9 g (58%) of the target material obtained as a brown oily material.

(2) (±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(3-methoxyphenyl)ethylamine

2.0 ml of concentrated hydrochloric acid was added to 10 ml of a methanol solution of 0.88 g of (±)-N,N-dimethyl-1-[3-(methoxymethoxy)phenyl]-2-(3-methoxyphenyl)ethylamine and the mixture heated and refluxed for 2 hours. After cooling, water and aqueous sodium bicarbonate solution were added to the reaction liquid and then extraction performed with ethyl acetate. After washing with water and saturated

salt solution, and then drying with anhydrous magnesium sulphate, the solvent was distilled off. The residue was washed with isopropyl ether, and there was obtained 0.69 g (91%) of the target compound as pale brown crystals. mp 142-143°C

(3) (±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(3-methoxyphenyl)ethylamine hydrochloride

1.0 ml of 22% HCl-MeOH was added to 12 ml of an ether solution of 0.5 g of (±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(3-methoxyphenyl)ethylamine and then the solvent distilled off. The crystals which precipitated were washed with ether, and then filtered off and 0.48 g (89%) of the target material obtained as colourless crystals.

mp 153-158°C (decomposes)

IR (KBr, $cm^{-1}$): 3200, 1608, 1589, 1489, 1263, 1040, 789

Elemental analysis: $C_{18}H_{23}NO_2.HCl.1/4H_2O$ *{sic}*[iv]

theoretical (%): C = 65.37, H = 6.94, N = 4.48

measured (%): C = 65.29, H = 7.08, N = 4.41

The compounds in Examples 67 to 70 below were synthesised in the same way as in Example 66.

Example 67

<u>(±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-phenylethylamine hydrochloride</u> mp: 216-217°C

IR (KBr, $cm^{-1}$): 3200, 2950, 1590, 1493, 1480, 1456, 1318, 1281, 1231, 897, 794, 704

Elemental analysis: $C_{16}H_{19}NO.HCl.1/4H_2O$

theoretical (%): C = 68.08, H = 7.32, N = 4.96

measured (%): C = 68.27, H = 7.61, N = 5.09

Example 68

(±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(p-tolyl)ethylamine hydrochloride mp: 173-175°C

IR (KBr, $cm^{-1}$): 3200, 2950, 2750, 1592, 1480, 1400, 1283, 999, 899, 806, 704

Elemental analysis: $C_{17}H_{21}NO.HCl$

theoretical (%): C = 69.97, H = 7.60, N = 4.80

measured (%): C = 69.69, H = 7.83, N = 5.00

Example 69

(±)-N,N-dimethyl-2-(4-chlorophenyl)-1-(3-hydroxyphenyl)-ethylamine hydrochloride

mp: 166-168°C

IR (KBr, $cm^{-1}$): 3200, 2950, 2750, 1592, 1493, 1460, 1281, 1235, 1094, 1017, 899, 818

Elemental analysis: $C_{16}H_{18}ClNO.HCl.1/4H_2O$

theoretical (%): C = 60.67, H = 6.20, N = 4.42

measured (%): C = 60.79, H = 6.41, N = 4.38

Example 70

(±)-N,N-dimethyl-2-(3-fluorophenyl)-1-(3-hydroxyphenyl)-ethylamine hydrochloride

mp: 205-207°C

IR (KBr, $cm^{-1}$): 3080, 2600, 1616, 1588, 1489, 1327, 1250, 1142, 938, 799, 704

Elemental analysis: $C_{16}H_{18}FNO.HCl$.

theoretical (%): C = 64.97, H = 6.47, N = 4.74

measured (%): C = 64.55, H = 6.31, N = 4.78

Example 71

(±)-N-allyl-N-methyl-2-(4-ethoxycarbonylphenyl)-1-(3-hydroxyphenyl)ethylamine hydrochloride

The target compound was obtained in the same way as in Example 1 using the compound obtained in Reference Example-7.

mp: 94-96°C

IR (KBr, $cm^{-1}$): 1715, 1460, 1281

Elemental analysis: $C_{21}H_{25}NO_3.HCl.3/5H_2O$

theoretical (%): C = 65.22, H = 7.09, N = 3.62

measured (%): C = 65.42, H = 7.39, N = 3.78

Example 72

(±)-N,N-diallyl-2-(4-ethoxycarbonylphenyl)-1-(3-hydroxyphenyl)ethylamine hydrochloride

The target compound was obtained in the same way as in Example 1 (2) and (3) using the compound obtained in Reference Example 8.

mp: 72-76°C

IR (KBr, $cm^{-1}$): 1717, 1458, 1281

Elemental analysis: $C_{23}H_{27}NO_3.HCl.2/5H_2O$

theoretical (%): C = 67.52, H = 7.10, N = 3.42

measured (%): C = 67.50, H = 7.26, N = 3.50

Example 73

(±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-[4-(methoxyacetyl)-phenyl]ethylamine hydrochloride

Synthesis of (±)-N,N-dimethyl-2-[4-(methoxyacetyl)phenyl]-1-(3-methoxymethoxyphenyl)ethylamine

Under a current of argon, 10 ml of a dry tetrahydrofuran solution of 1.00 g of (±)-N,N-dimethyl-2-(4-bromophenyl)-1-(3-methoxymethoxyphenyl)ethylamine, synthesised in the same way as in Reference Example 3 and Example 1 (1), was cooled in a dry ice/acetone bath, and then 1.9 ml of n-butyllithium (1.6M n-hexane solution) added dropwise. After stirring for 30 minutes, 2 ml of a dry tetrahydrofuran solution of 0.20 g of methoxyacetonitrile

was slowly added dropwise, and stirring carried out for a further 30 minutes. The dry ice/acetone bath was removed and the temperature raised to room temperature, after which the reaction liquid was poured into 10% citric acid. The pH was adjusted to 8 by the addition of saturated $NaHCO_3$ and then extraction carried out with ethyl acetate. After drying with anhydrous $MgSO_4$, the solvent was distilled off under reduced pressure. The brown-coloured oily material obtained was purified by silica gel column chromatography ($CHCl_3$ : MeOH = 50 : 1) and 0.174 g of the desired compound obtained as a pale yellow oily material. Subsequently, the target compound was obtained in the same way as in Example 1 (2) and (3).

IR (KBr, $cm^{-1}$): 3200, 1696, 1607, 1460, 1126

Elemental analysis: $C_{19}H_{23}NO_3.HCl.1/2H_2O$

theoretical (%): C = 63.59, H = 7.02, N = 3.90

measured (%): C = 63.44, H = 7.07, N = 4.19

Example 74

(+)-N,N-dimethyl-1-(3-acetoxyphenyl)-2-(2-naphthyl)-ethylamine hydrochloride

0.3 g of the (+)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(2-naphthyl)ethylamine obtained in Example 7 was dissolved in 3 ml of pyridine, then 3 ml of acetic anhydride added and stirring conducted for 1 hour at room temperature. The reaction liquid was poured into ice water, and then made alkaline by the addition of saturated aqueous $NaHCO_3$ solution. Extraction was conducted with ethyl acetate and,

after washing with water, drying was carried out with $MgSO_4$. The solvent was distilled off and the residue purified by column chromatography ($CHCl_3$ : MeOH = 100 : 1), giving 0.22 g of a pale yellow oily material. This was dissolved in 2 ml of ethyl acetate, then 21% HCl-AcOEt solution added, and 0.14 g of (S)-(+)-1-(3-acetoxyphenyl)-N,N-dimethyl-2-(2-naphthyl)ethylamine hydrochloride obtained as a colourless powder.

mp: 161-164°C

IR (KBr, $cm^{-1}$): 2556, 2463, 1763, 1201

Elemental analysis: $C_{23}H_{23}NO_2.HCl.1/4H_2O$ *{sic}*

theoretical (%): C = 70.58, H = 6.60, N = 3.74

measured (%): C = 70.57, H = 6.70, N = 3.84

$[\alpha]^{20}_D$ = 120.13 (c = 0.606, methanol)

The compounds in Examples 75 to 78 were obtained in the same way as in Example 74.

Example 75

(-)-N,N-dimethyl-1-(3-acetoxyphenyl)-2-(4-ethoxycarbonyl-phenyl)ethylamine hydrochloride

IR (KBr, $cm^{-1}$): 1767, 1715, 1279, 1203

Elemental analysis: $C_{21}H_{25}NO_4.HCl.1/4H_2O$

theoretical (%): C = 63.63, H = 6.74, N = 3.53

measured (%): C = 63.63, H = 6.59, N = 3.77

$[\alpha]^{20}_D$ = -119.57 (c = 1.027, methanol)

Example 76

(-)-N,N-dimethyl-1-(3-acetoxyphenyl)-2-(4-propionylphenyl)-ethylamine hydrochloride

mp: 200-201°C

IR (KBr, $cm^{-1}$): 2938, 2460, 1763, 1686, 1225, 1200

Elemental analysis: $C_{21}H_{25}NO_3$.HCl

theoretical (%): C = 67.10, H = 6.97, N = 3.73

measured (%): C = 66.81, H = 6.98, N = 3.82

Example 77

(+)-N,N-dimethyl-1-(3-acetoxyphenyl)-2-(4-methoxymethyl-phenyl)ethylamine hydrochloride

mp: 182-186°C

IR (KBr, $cm^{-1}$): 2463, 1769, 1192, 1098, 702

Elemental analysis: $C_{20}H_{25}NO_3$.HCl

theoretical (%): C = 66.02, H = 7.20, N = 3.85

measured (%): C = 66.01, H = 7.27, N = 3.93

$[\alpha]^{20}_D$ = 101.31 (c = 0.531, methanol) (93%ee)

Example 78

(+)-N,N-dimethyl-1-(3-acetoxyphenyl)-2-(4-ethoxymethyl-phenyl)ethylamine hydrochloride

mp: 143-146°C

IR (KBr, $cm^{-1}$): 2652, 1763, 1194, 1096, 700

Elemental analysis: $C_{21}H_{27}NO_3.HCl$

theoretical (%): C = 66.74, H = 7.47, N = 3.71

measured (%): C = 66.58, H = 7.45, N = 3.73

$[\alpha]^{20}_D$ = 102.63 (c = 0.456, methanol) (74%ee)

Example 79

(+)-N,N-dimethyl-2-(2-naphthyl)-1-(3-trimethylacetyloxy-phenyl)ethylamine hydrochloride

0.3 g of the (+)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(2-naphthyl)ethylamine obtained in Example 7 was dissolved in 3 ml of tetrahydrofuran, then 0.2 g of triethylamine added, followed by the dropwise addition at room temperature of a tetrahydrofuran solution of 0.14 g of pivaloyl chloride, after which stirring was carried out for 24 hours. Water was added to the reaction liquid and then extraction carried out with ethyl acetate. After washing the extraction liquid with water, it was dried with anhydrous $MgSO_4$ and then the solvent distilled off. The residue obtained was purified by column chromatography ($CHCl_3$ : MeOH = 100 : 1) and 0.25 g of a pale yellow oily material obtained (yield 65%). This was dissolved in 2 ml of ethyl acetate, then 21% HCl-AcOEt solution added and 0.21 g of

(+)-N,N-dimethyl-2-(2-naphthyl)-1-(3-trimethylacetyloxyphenyl)ethylamine hydrochloride obtained as a colourless powder.

mp: 175-177°C

IR (KBr, $cm^{-1}$): 2972, 1750, 1149, 1113

Elemental analysis: $C_{25}H_{29}NO_2.HCl.1/5H_2O$

theoretical (%): C = 72.26, H = 7.37, N = 3.37

measured (%): C = 72.27, H = 7.33, N = 3.65

$[\alpha]^{20}_D$ = 106.29 (c = 0.747, methanol)

The compounds in Examples 80 and 81 were obtained in the same way as in Example 79.

Example 80

(+)-N,N-dimethyl-2-(4-methoxymethylphenyl)-1-(3-trimethylacetyloxyphenyl)ethylamine hydrochloride

mp: 124-127°C

IR (KBr, $cm^{-1}$): 2973, 1746, 1150, 1117

Elemental analysis: $C_{23}H_{31}NO_3.HCl$

theoretical (%): C = 68.05, H = 7.95, N = 3.45

measured (%): C = 67.75, H = 7.94, N = 3.55

$[\alpha]^{20}_D$ = 91.44 (c = 0.807, methanol) (93%ee)

Example 81

(+)-N,N-dimethyl-2-(4-ethoxymethylphenyl)-1-(3-trimethylacetyloxyphenyl)ethylamine hydrochloride

mp: 155-158°C

IR (KBr, $cm^{-1}$): 2973, 1755, 1456, 1144, 1113

Elemental analysis: $C_{24}H_{33}NO_3.HCl$

theoretical (%): C = 68.64, H = 8.16, N = 3.34

measured (%): C = 68.51, H = 8.31, N = 3.36

$[\alpha]^{20}_D$ = 86.88 (c = 0.755, methanol) (74%ee)

Example 82

(+)-N,N-dimethyl-1-(3-acetylsalicyloyloxyphenyl)-2-(4-ethoxymethylphenyl)ethylamine hydrochloride

300 mg of (+)-N,N-dimethyl-2-(4-ethoxymethylphenyl)-1-(3-hydroxyphenyl)ethylamine obtained in Example 46 was dissolved in 5 ml of methylene chloride and then 0.7 ml of triethylamine added. While stirring and ice-cooling, there was slowly added dropwise a 3 ml methylene chloride solution of 218 mg of acetylsalicyloyl chloride. Subsequently, after stirring overnight at room temperature, the reaction liquid was washed with water, and then dried with anhydrous magnesium sulphate. After removing the drying agent, the methylene chloride was distilled off. The residue obtained was purified by silica gel column chromatography (chloroform : methanol = 50 = 1), and 420 mg

of the target compound obtained as a colourless oily material.

IR (KBr, $cm^{-1}$): 2975, 1769, 1774, 1485, 1231, 1194, 1053, 756

Elemental analysis: $C_{28}H_{31}NO_5.HCl.1/4H_2O$

theoretical (%): C = 66.92, H = 6.52, N = 2.79

measured (%): C = 66.97, H = 6.74, N = 3.04

Example 83

(+)-N,N-dimethyl-2-(4-ethoxymethylphenyl)-1-(3-N-n-propylcarbamoyloxyphenyl)ethylamine hydrochloride

170 mg of n-propylisocyanate was added to 300 mg of the (+)-N,N-dimethyl-2-(4-ethoxymethylphenyl)-1-(3-hydroxyphenyl)ethylamine obtained in Example 46, then dissolved in 5 ml of toluene, and heating and refluxing performed for 4 hours. The toluene was distilled off, and the residue purified by silica gel chromatography (chloroform : methanol = 50 : 1), and 370 mg of the desired compound obtained as a colourless oily material. This was dissolved in 6 ml of ethyl acetate, then 2 ml of 21% HCl-AcOEt solution added and the solvent distilled off under reduced pressure, to produce the hydrochloride.

IR (KBr, $cm^{-1}$): 2963, 1730, 1518, 1487, 1456, 1225, 1098, 700

Elemental analysis: $C_{23}H_{32}N_2O_3.HCl.1/2H_2O$

theoretical (%): C = 64.25, H = 7.97, N = 6.51

measured (%): C = 64.11, H = 8.31, N = 6.56

Example 84

(+)-N,N-dimethyl-1-(3-N,N-dimethylcarbamoyloxyphenyl)-2-(4-ethoxymethylphenyl)ethylamine hydrochloride

45.2 mg of 60% sodium hydride was suspended in 1 ml of tetrahydrofuran, and then 3 ml of a tetrahydrofuran solution of 338 mg of the (+)-N,N-dimethyl-2-(4-ethoxymethylphenyl)-1-(3-hydroxyphenyl)ethylamine obtained in Example 46 was added. After stirring for 10 minutes at room temperature, 2 ml of a tetrahydrofuran solution of 146 mg of N,N-dimethylcarbamoyl chloride was added dropwise, and then the mixture stirred for 1 hour. Following the completion of the reaction, the tetrahydrofuran was distilled off under reduced pressure, and 5 ml of water added to the residue, after which extraction was carried out with ethyl acetate (5 ml × 3). The organic layer was dried with anhydrous magnesium sulphate, and then the solvent distilled off under reduced pressure. The residue was purified by silica gel column chromatography and 410 mg of (+)-N,N-dimethyl-1-(3-N,N-dimethylcarbamoyloxyphenyl)-2-(4-ethoxymethylphenyl)ethylamine obtained. This was dissolved in 6 ml of ethyl acetate, and 2 ml of 21% hydrochloric acid/ethyl acetate solution added. After distilling off the solvent under reduced pressure, ether was added to the residue and crystallization effected. The crystals were filtered off using a glass filter, then dried, and 308 mg of the target material obtained as colourless crystals.

mp: 109-110°C

IR (KBr, $cm^{-1}$): 2870, 1725, 1387, 1237, 1171, 1117,

Elemental analysis: $C_{22}H_{30}N_2O_3.HCl.1/2H_2O$

theoretical (%): C = 63.53, H = 7.75, N = 6.73

measured (%): C = 63.49, H = 7.71, N = 6.83

The following compound was synthesised in the same way as in Example 84

Example 85

(+)-N,N-dimethyl-1-(3-N,N-dimethylcarbamoyloxyphenyl)-2-(4-methoxymethylphenyl)ethylamine hydrochloride

IR (KBr, $cm^{-1}$): 2932, 1721, 1389, 1238, 1171

Elemental analysis: $C_{21}H_{28}N_2O_3.HCl.1/2H_2O$

theoretical (%): C = 62.75, H = 7.52, N = 6.97

measured (%): C = 62.58, H = 7.55, N = 6.90

$[\alpha]^{20}_D$ = 96.35 (c = 1.071, methanol) (93%ee)

Example 86

(+)-N,N-dimethyl-1-(3-ethoxycarbonyloxyphenyl)-2-(4-methoxymethylphenyl)ethylamine hydrochloride

62 mg of 60% sodium hydride was suspended in 1 ml of dry tetrahydrofuran under a current of argon, and then 3 ml of a dry tetrahydrofuran solution of 500 mg of the (+)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(4-methoxymethylphenyl)-ethylamine obtained in Example 47 added dropwise. After

stirring for 10 minutes at room temperature, 2 ml of a dry tetrahydrofuran solution of ethyl chloroformate was slowly added dropwise. After stirring for 30 minutes at room temperature, the reaction liquid was diluted with water, and extracted with ethyl acetate. The organic layer was washed with water and then dried with anhydrous $MgSO_4$, after which the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$ : MeOH = 100 : 1), and 544 mg of the desired compound obtained as a colourless oily material. The oily material thus obtained was converted to the hydrochloride with 21% HCl-AcOEt solution, and colourless crystals obtained.

mp: 140-143°C

IR (KBr, $cm^{-1}$): 2651, 1757, 1262, 1229

Elemental analysis: $C_{21}H_{27}NO_4.HCl$

theoretical (%): C = 64.03, H = 7.16, N = 3.56

measured (%): C = 64.01, H = 7.08, N = 3.66

$[\alpha]^{20}_D$ = 93.93 (c = 0.747, methanol) (93%ee)

The following compound was obtained in the same way as in Example 86.

Example 87

(+)-N,N-dimethyl-1-(3-ethoxycarbonyloxyphenyl)-2-(4-ethoxymethylphenyl)ethylamine hydrochloride

mp: 144-145°C

IR (KBr, $cm^{-1}$): 2977, 1759, 1614, 1371, 1260, 1229, 1098, 781

Elemental analysis: $C_{22}H_{29}NO_4.HCl.1/2H_2O$

theoretical (%): C = 63.37, H = 7.49, N = 3.36

measured (%): C = 63.61, H = 7.52, N = 3.38

Example 88

(+)-N,N-dimethyl-1-[3-(2-aminobenzoyloxy)phenyl]-2-(4-ethoxymethylphenyl)ethylamine dihydrochloride

122 mg of 4-dimethylaminopyridine was added to a 3 ml N,N-dimethylformamide solution of 300 mg of the (+)-N,N-dimethyl-2-(4-ethoxymethylphenyl)-1-(3-hydroxyphenyl)ethylamine obtained in Example 46 and 196 mg of anhydrous isatoic acid, and then the mixture heated for 4 hours at 80°C. After leaving to cool to room temperature, water was added to the reaction liquid and extraction performed with ethyl acetate. The organic layer was then washed with water and dried with anhydrous $MgSO_4$, after which the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$ : MeOH = 40 : 1), and 407 mg of the desired compound obtained as a colourless oily material. The oily material thus obtained was converted to the hydrochloride with 21% HCl-AcOEt solution.

IR (KBr, $cm^{-1}$): 2973, 1740, 1489, 1229, 749

Elemental analysis: $C_{26}H_{30}N_2O_3.2HCl.1/2H_2O$

theoretical (%): C = 62.40, H = 6.65, N = 5.60

measured (%): C = 62.26, H = 6.86, N = 5.63

$[\alpha]^{20}_{D}$ = 99.08 (c = 0.547, methanol)

Example 89

(±)-N,N-dimethyl-1-(3-hydroxy-4-methylphenyl)-2-(4-ethoxymethylphenyl)ethylamine hydrochloride

(1) 2-hydroxy-4-(N-methoxy-N-methylcarbamoyl)toluene

7.00 g of 3-hydroxy-4-methylbenzoic acid and 4.94 g of N,O-dimethylhydroxylamine hydrochloride were dissolved in 45 ml of N,N-dimethylformamide, and 8.9 ml of N,N-diisopropylethylamine added. After stirring for 10 minutes, the reaction liquid was ice cooled and 8.07 g of diethylphosphoryl cyanide added dropwise, followed by 8.0 ml of N,N-diisopropylethylamine. The temperature was raised to room temperature and stirring carried out for 12 hours, after which water was added and then extraction performed with ethyl acetate. The organic layer was washed with 10% hydrochloric acid, saturated aqueous $NaHCO_3$ solution and water, and then dried with anhydrous $MgSO_4$. After distilling off the solvent under reduced pressure, 8.84 g of an orange-coloured oily material was obtained.

(2) 3-(methoxymethoxy)-4-methylbenzaldehyde

8.84 g of 2-hydroxy-4-(N-methoxy-N-methylcarbamoyl)toluene and 8.7 ml of N,N-diisopropylethylamine were dissolved in 45 ml of dichloromethane and, while ice cooling, a 20 ml

dichloromethane solution of 3.8 ml of chloromethyl methyl ether added dropwise. After stirring for 12 hours at room temperature, the reaction liquid was poured into water and the organic layer separated off. After drying with anhydrous $MgSO_4$, the solvent was driven off and 7.12 g of 2-(methoxymethoxy)-4-(N-methoxy-N-methylcarbamoyl)toluene obtained as an orange-coloured oily material. Under a current of argon, 7.12 g of the oily material was dissolved in 70 ml of anhydrous tetrahydrofuran and then cooled using a dry ice/acetone bath. 45 ml of diisobutylaluminium hydride (1M toluene solution) was slowly added dropwise and, after stirring for 1 hour, water was added. The insoluble material was filtered off, after which the organic layer was separated and dried with anhydrous $MgSO_4$. The solvent was then distilled off, and the residue purified by silica gel column chromatography (n-hexane : ethyl acetate = 4 : 1), and 4.93 g of pale yellow oily material obtained.

(3) (±)-N,N-dimethyl-1-(3-hydroxy-4-methylphenyl)-2-(4-ethoxymethylphenyl)ethylamine hydrochloride

Using the 3-(methoxymethoxy)-4-methylbenzaldehyde, the target material was obtained in the same way as in Reference Example 3 and Example 1.

mp: 203-204°C

IR (KBr, $cm^{-1}$): 3110, 2975, 1455, 1271, 1123

Elemental analysis: $C_{20}H_{27}NO_2.HCl$

theoretical (%): C = 68.65, H = 8.07, N = 4.00

measured (%): C = 68.70, H = 7.95, N = 4.11

Example 90

(±)-N,N-dimethyl-1-(3-chloro-5-hydroxyphenyl)-2-(4-ethoxymethylphenyl)ethylamine hydrochloride

(1) 3-chloro-5-methoxyphenyl trifluoromethanesulphonate

15.00 g of 3-chloro-5-methoxyphenol was dissolved in pyridine and, while ice cooling, 29.36 g of trifluoromethanesulphonic anhydride was added dropwise. The temperature was raised to room temperature and, after 2 hours stirring, the reaction liquid was diluted with water and then extraction performed with ether. After washing with 10% hydrochloric acid and then water, drying was performed with anhydrous $MgSO_4$, after which the solvent was distilled off and 27.34 g of a pale yellow coloured oily material obtained.

(2) Methyl 3-chloro-5-methoxybenzoate

27.34 g of the 3-chloro-5-methoxyphenyl trifluoromethanesulphonate, 2.11 g of palladium(II) acetate, 3.88 g of 1,3-bis(diphenylphosphino)propane, 35 ml of triethylamine, 200 ml of methanol, 100 ml of 1,2-dichloroethane and 180 ml dimethylsulphoxide were mixed together, and carbon monoxide bubbled through. The temperature was raised to 70°C and, after stirring for 2 hours, the bubbling was halted and stirring continued for a further 12 hours. Water was added to the reaction liquid and then extraction conducted with ether. After washing with 10% hydrochloric acid, saturated

aqueous $NaHCO_3$ solution, and water, drying was conducted with anhydrous $MgSO_4$, and then the solvent distilled off. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 4 : 1), and 17.67 g of a pale yellow oily material obtained.

(3) 3-chloro-5-hydroxybenzoic acid

16.67 g of the methyl 3-chloro-5-methoxybenzoate was dissolved in 160 ml of acetic acid, and then 160 ml of 48% hydrobromic acid added. After stirring for 9 hours at 120°C, the reaction liquid was poured into water. The crystals which were deposited were filtered off. The mother liquor was extracted with ether : ethyl acetate (1 : 1), after which the solvent was distilled off and brown crystals obtained. After combining with the aforesaid crystals, 100 ml of 47% hydrobromic acid and 160 ml of acetic acid were added, and stirring carried out for a further 4 hours at 130°C. After allowing the reaction liquid to cool, ice-water was added and the crystals which precipitated were filtered off. 9.84 g of pale brown crystals were obtained.

(4) (±)-N,N-dimethyl-1-(3-chloro-5-hydroxyphenyl)-2-(4-ethoxymethylphenyl)ethylamine hydrochloride

The target compound was obtained in the same way as in Example 89 using the 3-chloro-5-hydroxybenzoic acid.

IR (KBr, $cm^{-1}$): 2975, 1599, 1456, 1283, 1100

Elemental analysis: $C_{19}H_{24}ClNO_2.HCl.1/5H_2O$

theoretical (%): C = 61.03, H = 6.85, N = 3.75

measured (%): C = 60.92, H = 6.90, N = 3.93

Example 91

(±)-N,N-dimethyl-1-(2-chloro-5-hydroxyphenyl)-2-(4-ethoxymethylphenyl)ethylamine hydrochloride

The 2-chloro-5-hydroxybenzaldehyde employed here as the starting material was synthesised in accordance with the method of H.H. Hodgson *et al* [J. Chem. Soc., 149 (1926)] and, using this, the target material was obtained in the same way as in Reference Example 3 and Example 1.

IR (KBr, $cm^{-1}$): 2975, 1480, 1294, 1098, 818

Elemental analysis: $C_{19}H_{24}ClNO_2.HCl.1/2H_2O$

theoretical (%): C = 60.16, H = 6.90, N = 3.69

measured (%): C = 60.36, H = 6.90, N = 3.88

Example 92

(±)-N,N-dimethyl-1-(4-fluoro-3-hydroxyphenyl)-2-(4-ethoxymethylphenyl)ethylamine hydrochloride

The 4-fluoro-3-hydroxybenzaldehyde employed here as the starting material was synthesised in accordance with the method of K.L. Kirk *et al* [J. Med. Chem., 29, 1982 (1986)] and, using this, the target material was obtained in the same way as in Reference Example 3 and Example 1.

IR (KBr, $cm^{-1}$): 3569, 1509, 1289, 1119

Elemental analysis: $C_{19}H_{24}FNO_2.HCl.1/2H_2O$

theoretical (%): C = 62.89, H = 7.22, N = 3.86

measured (%): C = 62.80, H = 7.13, N = 4.06

Example 93

(±)-N,N-dimethyl-1-(3-hydroxyphenyl)-2-(4-hydroxyphenyl)-ethylamine hydrochloride

The compound obtained in Example 1 (2) was heat-treated with hydrobromic acid, and then the target material obtained by forming the hydrochloride in the normal manner.

mp: 168-171°C

IR (KBr, $cm^{-1}$): 3200, 1615, 1592, 1460, 1516, 1460, 1266, 1229

Elemental analysis: $C_{16}H_{19}NO_2.HCl.2/3H_2O$

theoretical (%): C = 62.84, H = 6.70, N = 4.58

measured (%): C = 62.81, H = 7.09, N = 4.44

Experimental Example 1

Binding Assay (opioid receptor subtype selectivity)

Method:

Rat brain (excluding the cerebellum) or guinea pig cerebellum was homogenized in a Tris-HCl buffer solution (50 mM, pH 7.4) and centrifuging performed for 20 minutes

at 40,000g, after which the sediment suspended in buffer solution was used as the membrane specimen.

The [$^3$H] binding assay was carried out, in the case of the μ-opioid receptor, on the basis of the binding of [$^3$H]DAMGO ([D-Ala$^2$,MePhe$^4$,Gly-ol$^5$]enkephalin 2 nM) to the rat brain membrane specimen; in the case of the δ-opioid receptor, on the basis of the binding of [$^3$H]DPDPE-Cl (cyclic([D-Pen$^2$,p-Cl-Phe$^4$,D-Pen$^5$]enkephalin) 1 nM) to the rat brain membrane specimen; and in the case of the κ-opioid receptor, on the basis of the binding of [$^3$H]EKC (ethylketocyclazocine 0.5 nM) or [$^3$H]Cl-977 [(5R)-(5α,7α,8β)-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro-[4,5]dec-8-yl]-4-benzofuran-acetamide monohydrochloride 0.5 nM) to the guinea pig cerebellum membrane specimen. The inhibitory action of the material under test on the binding of these was investigated and the affinities of the material under test for each of the opioid receptor subtypes (the Ki values) determined. As control compounds, there were used the narcotic analgesic morphine which is a μ-opioid receptor agonist, DPDPE (reagent) which is a peptide type δ-agonist, the analgesic Lefetamine, and Naltrindole (reagent) which is a δ-antagonist. The results are shown in Table 1.

Experimental Example 2

Binding Assay (sodium coefficient)

Method

Rat brain (excluding the cerebellum) was homogenized in a Tris-HCl buffer solution (50 mM, pH 7.4) and centrifuging

carried out at 40,000g for 20 minutes, after which the sediment suspended in buffer solution was used as the membrane specimen.

The inhibitory action of the material under test on the binding of [$^3$H]Naltrindole (0.2 nM) to the rat brain membrane specimen was investigated in the presence or absence of $Na^+$ (100 mM). The sodium coefficient of the material under test was found by dividing the Ki value of the material under test in the presence of $Na^+$ by the Ki value in the absence of $Na^+$. The results are shown in Table 1.

Table 1: Inhibitory Action on Opioid Receptor Binding

| Drug under Test (Example No.) | pKi (M) | | | δ-Selectivity (Ki value ratio) | | Na Coefficient |
|---|---|---|---|---|---|---|
| | μ | δ | κ | μ/δ | κ/δ | |
| Example 7 (+) isomer | 5.90 | 8.15 | 5.97 | 177 | 151 | 8.5 |
| Example 12 (+) isomer | 6.56 | 8.38 | 6.66 | 67 | 53 | 2.9 |
| Example 24 (-) isomer | 6.89 | 8.50 | 6.69 | 41 | 66 | 8.4 |
| Example 44 (+) isomer | 6.04 | 8.57 | 6.42 | 340 | 143 | 3.3 |
| Example 46 (+) isomer | 6.27 | 8.06 | 6.32 | 61 | 54 | 3.0 |
| Morphine | 8.18 | 6.64 | 6.74 | 0.03 | 0.8 | - |
| DPDPE | 6.03 | 8.17 | <5.5 | 138.0 | >500 | 12.4 |
| Lefetamine | 6.72 | 5.93 | 5.69 | 0.16 | 1.7 | - |
| Naltrindole | 7.63 | 9.72 | 7.96 | 123.0 | 57.5 | 0.94 |

The compounds of the present invention showed high affinity for the δ-opioid receptor, with Ki values of no more than 10 nM. Furthermore, when compared to the μ-opioid receptors, there was exhibited a 41-340 fold δ-selectivity. This constitutes a high δ-affinity and selectivity, equal to or greater than in the case of the peptide DPDPE. Since

both the δ-affinity and selectivity are high, this suggests that the compounds of the present invention can be used as immunoactivators and/or as urinary frequency/urinary incontinence treatment agents.

It is known that, in opioid receptor binding tests, agonist affinity is lowered by the presence of sodium ions and antagonist affinity is unchanged. The compounds of the present invention exhibited sodium coefficients of 2.9 to 8.5 and their affinity was lowered by the presence of sodium ions, suggesting that they have a δ-agonist action. The sodium coefficient of the control compound DPDPE (a δ-agonist), at 12.4, indicated a reduction in affinity resulting from the presence of sodium ions, whereas that of the Naltrindole (a δ-antagonist) showed a value of less than 1, indicating no lowering of affinity.

Experimental Example 3

Inhibitory Action on cAMP Production in δ-Opioid Receptor Expressing Cells

Cloned Chinese hamster ovary epithelial cells expressing human δ-opioid receptor were employed. 100 μM of water-soluble forskolin was added to a medium containing 5 mM IBMX in which said cells had been cultured and incubation carried out (37°C, 3 minutes). Ice-cooled Tris/EDTA buffer solution was added and the reaction halted. Levels of cAMP produced within the cells were determined by measuring the inhibitory effect on [3H]cAMP binding to cAMP-dependent protein kinase. The material under test was jointly

present in the reaction liquid and the action in terms of cAMP production investigated. It was found, as a result, that the Example 20 (-)isomer and the Example 34 (+)isomer exhibited an inhibitory action on cAMP production, with $IC_{50}$ values of 16.7 and 2.8 nM respectively, thereby showing that they possessed strong δ-agonist activity.

Experimental Example 4

Acute Toxicity Test

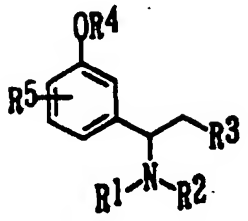
Seven week old male SD-type rats were used in groups of 4 animals. After having withheld food from the previous day (16-18 hours before), the compound of Example 46 was orally administered using a gastric probe, and observation of the number of cases of mortality over the 7 days thereafter was carried out. As a result, on administering 250 mg/kg, no cases of mortality were observed and no abnormal findings were noted.

Industrial Utilization Potential

When compared with control compounds, the compounds of the present invention bind extremely strongly and selectively to the δ-opioid receptor and exhibit agonist activity, so they can be employed as non-addictive analgesics, immuno-activators and urination controlling agents, for the treatment and prevention of various types of pain/ache, immunocompromise, urinary frequency and incontinence.

## Scope of Claims

1. Compounds represented by the following general formula [I]




[I]

and their pharmaceutically acceptable salts, or solvates thereof.

In the formula, $R^1$ and $R^2$ are the same or different, and represent alkyl groups or alkenyl groups. $R^3$ represents an optionally-substituted aryl group or an optionally-substituted aromatic heterocyclic group. Said aromatic heterocyclic group will include at least one heteroatom selected from the group comprising nitrogen, oxygen and sulphur. $R^4$ represents hydrogen, acyl, alkoxycarbonyl, or optionally mono- or di-alkyl-substituted carbamoyl. $R^5$ represents hydrogen, halogen or alkyl.

2. Compounds according to Claim 1 where $R^3$ is an aryl group or aromatic heterocyclic group, which is unsubstituted or is substituted with alkyl, aryl, alkoxy, aryloxy, alkylthio, hydroxyalkyl, alkoxyalkyl, trifluoroalkyl, acyl, hydroxy, halogen, cyano, carboxy, optionally halogen-substituted alkoxycarbonyl, or carbamoyl or sulphamoyl which may be substituted with one substituent or two identical or different substituents selected from the group comprising alkyl, aralkyl and alkoxy.

3. Compounds according to Claim 1 where $R^1$ and $R^2$ are alkyls with from 1 to 4 carbons, $R^3$ is a substituted aryl and $R^5$ is hydrogen.

4. Compounds according to Claim 1 or Claim 2 where $R^1$ and $R^2$ are methyls, $R^3$ is an aryl substituted with an alkoxy, alkoxyalkyl, acyl, alkoxycarbonyl or optionally fluorine-substituted naphthalyl *{sic}*, and $R^5$ is hydrogen.

5. Drugs wherein a compound according to Claims 1 to 4 is an active ingredient.

6. Drugs according to Claim 4 *{sic}* where the drug is a δ-opioid receptor agonist.

*Translator's notes*

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[i] The meaning of this sentence is not altogether clear. Perhaps what was intended here was "As examples of the alkyl or aryl groups comprising these substituent groups or contained within these substituent groups, there are those already cited above."

[ii] Perhaps both here and in Reference Example 3 No.37, sulphamoylphenyl was meant rather than sulphonylphenyl.

[iii] This does not correspond to the stated compound.

[iv] Should this not be $C_{17}$, etc?